ARCHIVES OF PATHOLOGY

VOLUME 19 APRIL 1935 NUMBER 4

LIGATION OF THE ARTERIES OF THE CONDUCTION SYSTEM

A SECOND ATTEMPT TO PRODUCE HEART BLOCK IN DOGS

EVAN M. BARTON, M.D.

CHICAGO

In a previous study of the sequences of ligation of the anterior septal artery of the dog's heart [1] it was found that a characteristic and often extensive infarct was produced in the interventricular septum which was not accompanied by any correspondingly constant changes in the electrocardiogram. Complete heart block occurred in one dog but was transient. Extrasystoles and tachycardia were common. Otherwise there was nothing in the tracings to indicate that the conduction system itself had been seriously damaged.[2] Further, it was found by microscopic examination of the atrioventricular node and bundle of His of these hearts that the amount of change due to infarction varied within wide limits and was not always proportionate to the degree of disturbance recorded electrocardiographically. The well known wide variations in the coronary circulation of the dog [3] undoubtedly account for some of these facts. In addition, one of the most obvious explanations for the results of that study was that the blood supply to the septum from behind, through the so-called "ramus septi fibrosi," or posterior septal artery, was still intact.[4] With this in mind, a series

From the Norman Bridge Pathological Laboratory, Rush Medical College.

1. Barton, E. M., and Greenwood, H. H.: Arch. Path. **16**:15, 1933.

2. Recent reports (Wilson, F. N.; Hill, I. G. W., and Johnston, F. D.: Am. Heart J. **9**:596, 1934. Hill, I. G. W., and Rothberger, C. J.: Ztschr. f. d. ges. exper. Med. **93**:420, 1934) indicate that heart block may follow ligation of the anterior septal artery with considerable regularity. In the experiments of Wilson, Hill and Johnston a block affecting branches or the main stem of the bundle was present forty-eight hours after ligation as revealed by electrocardiograms of two dogs. The tracings were made by direct and "semidirect" leads. Whether a block would have persisted beyond that period had the dogs been allowed to survive is uncertain. The report by Hill and Rothberger concerns only experiments in which dogs were not allowed to recover after ligation of the septal artery, so that proof of more than transient block is also lacking. In the work of Barton and Greenwood [1] as well as in the present study only the three standard leads were used.

3. Cohnheim, J., and von Schulthess-Rechberg, A.: Virchows Arch. f. path. Anat. **85**:503, 1881. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924.

4. Barton and Greenwood,[1] p. 15, footnote 4.

of experiments was planned with the aim of interrupting the circulation to the back of the septum and recording subsequent changes in conduction electrocardiographically after the animals recovered from the operation.

In most dogs this posterior septal artery arises from the terminal portion of the circumflex branch of the left coronary artery just proximal to the downward turn by which the latter forms its posterior descending branch.[5] The best approach was found to be through the sixth right intercostal space. With the dog lying almost prone, slightly on the left side, the proper region was exposed by pulling the heart to the right. With such a maneuver the right auricular appendage and the posterior branches of the coronary arteries coursing toward the apex along the back edge of the septum were brought into view. As the dissection was tedious it was found necessary to avoid prolonged traction on the heart because of the twisting of the great vessels, particularly the pulmonary veins and the inferior vena cava.

At its origin, the posterior septal branch has a diameter in the living animal of about 1 to 1.5 mm. It courses directly into the muscle of the septum at approximately a right angle to its parent stem and is not visible on the outside of the heart or in the subepicardial fat. Its ligation in the living dog was difficult especially because of the proximity of the coronary sinus and its larger tributaries, some of which nearly always tended to conceal the artery until hauled to one side with a guy suture. Accidental rupture of one of these veins not infrequently led to uncontrollable hemorrhage. With adequate assistance and rigorous aseptic precautions, the number of dogs surviving was such that about one third of those on which the operation was performed eventually were of experimental value. These dogs, seven in number, all had lesions produced by occlusion of the posterior septal artery (ramus septi fibrosi).

The infarcts produced were quite uniform in size and shape. On the left side of the septum their upper and posterior margin was at the place where the anterior mitral leaflet, having fused with the base of the aortic ring, joins the myocardium of the septum (fig. 1). From this place the lesions extended fanlike forward and inward for a distance of from 8 to 10 mm. The right side of the septum was affected less often than the left. When visible there, the infarcts lay under the tricuspid leaflet in the upper corner of the septum at the posterior margin. The youngest infarct was thirty-eight days old, and the oldest, ninety-one.

In electrocardiographic tracings made within twenty-four hours of the ligation, tachycardia, extrasystoles and inverted T waves in leads II and III were present (fig. 2 *A* and *C*). One tracing (fig. 2 *A*) was com-

5. Moore, R. A.: Am. Heart J. **5**:743, 1930.

patible with partial bundle-branch block. These changes tended to disappear as the infarcts became organized (fig. 2 *B* and *E*). After several weeks the only abnormality remaining was the configuration of the ST interval so often characteristic of previous myocardial infarction (fig. 2 *D*, *F* and *G*).

One concludes, therefore, that in these dogs occlusion of the blood supply to the conduction system from behind was insufficient to cause lasting changes in electrocardiograms, indicative of a lesion in the conduction system. This was not surprising, as a similar result followed

Fig. 1.—Heart of dog 4, fixed in Kaiserling's solution (30 Gm. of potassium acetate, 10 Gm. of potassium nitrate, 750 cc. of distilled water and 300 cc. of solution of formaldehyde), showing the left side of the interventricular septum forty-two days after the ligation of the posterior septal artery. The anterior mitral leaflet has been trimmed away. The scar typical of this condition is discernible just below and to the left of the line of junction between the auricle and ventricle in the upper right portion of the figure. The electrocardiogram of this dog is shown in figure 2 *E*.

occlusion of the anterior septal artery, a vessel considerably larger than the posterior.

The next step, of course, was to tie both the anterior and the posterior septal artery in the same dog. This was accomplished in two animals after many failures. Two operations, several weeks apart, were neces-

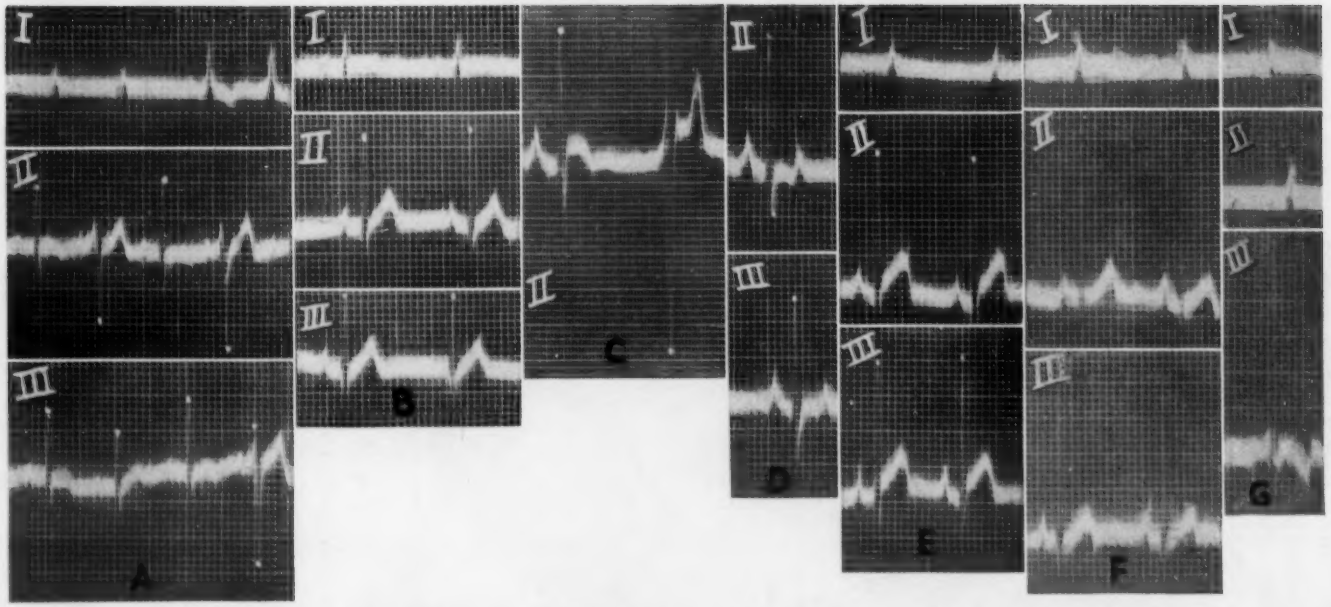

Fig. 2.—Electrocardiograms made after ligation of the posterior septal artery alone. Aside from elevation of the S T interval and an occasional extrasystole, the most noteworthy feature is the absence, in general, of conduction disturbances. *A* and *B* are electrocardiograms of dog 1, made twenty-four hours and thirteen days, respectively, after ligation. In *A*, certain Q R S complexes are aberrant; others are normal; in lead II the record is compatible with a 2 : 1 bundle-branch block. In *B*, these changes have disappeared. *C* and *D* are electrocardiograms of dog 3, made twenty-four hours and forty-one days, respectively, after ligation. *E* and *F* are electrocardiograms of dog 4, made three and forty-two days, respectively, after operation. The ordinates of all graphs indicate 0.04 second except in figure 2 *C*, where they represent 0.02 second. The standardization is 1 cm. per millivolt. The white dots indicate the limits of excursion. All the tracings were made with the dogs in the dorsal position and without the use of anesthesia or sedatives.

sary. In one of the two dogs that survived the anterior septal artery was ligated first, as in the experiments reported previously. A month after the first operation, when recovery was complete and the animal was again vigorous, the posterior branch to the septum was tied. For the other dog, the posterior artery was tied first [6] and forty days later the anterior. The choice of the initial operation was, in each instance, a matter of hazard.

The anatomic changes in these hearts were, as might be expected, the geometric sum of the two lesions typical of ligation of each vessel separately. The scar characteristic of occlusion of the anterior septal artery is spatulate and occupies the middle of the septum [7] (fig. 3). To

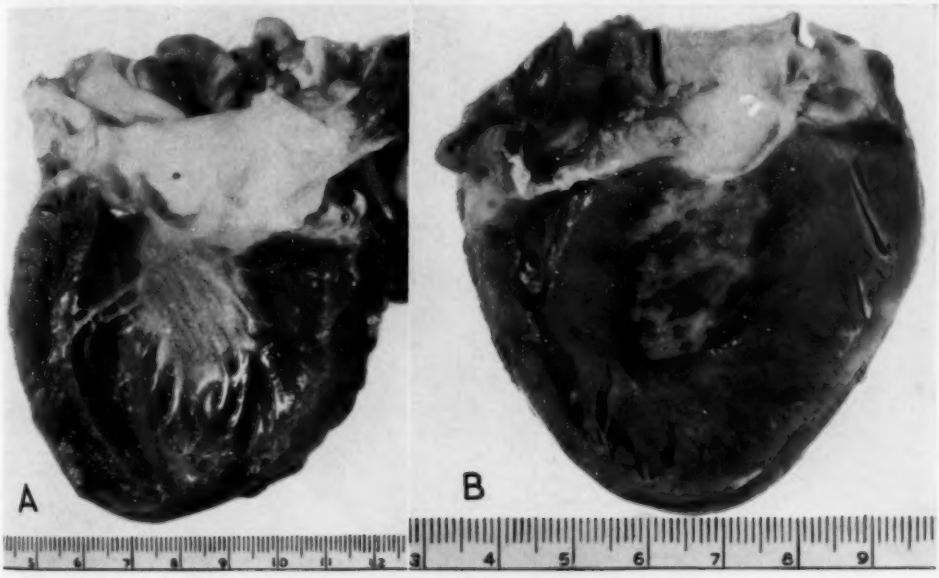

Fig. 3.—Infarcts typical of ligation of the anterior septal artery alone. *A*, left side of the interventricular septum five months after the artery was occluded (unfixed specimen). *B*, surface made by slicing the septum of another heart through its largest plane, viewed from the right. This lesion is three days old (fixation in Kaiserling's solution).

this was added the smaller, rounded infarct caused by occlusion of the posterior septal branch which has been described in a previous para-

6. During this operation it became necessary, owing to hemorrhage, to include the terminal part of the left circumflex branch in the ligature. At autopsy the lumen of the posterior septal branch as well as that of the larger trunk was found obliterated. But the ligation of the larger trunk at this point had not caused infarction of the outer wall of the heart, and the posterior infarct in this septum was atypical only because it was slightly larger than usual.

7. Barton and Greenwood,[1] figs. 1 and 2 A.

graph and is illustrated in figure 1. When present in a single heart, the combined lesion made a striking picture, for practically the entire base of the septum was involved (fig. 4).

The changes observed in electrocardiograms made with both vessels tied were not unlike those recorded after ligation of each artery singly (fig. 5).

In these two dogs, then, the circulation to the conduction system was interrupted by occluding both the anterior and the posterior nutrient artery. Tachycardia, extrasystoles and the usual signs of myocardial

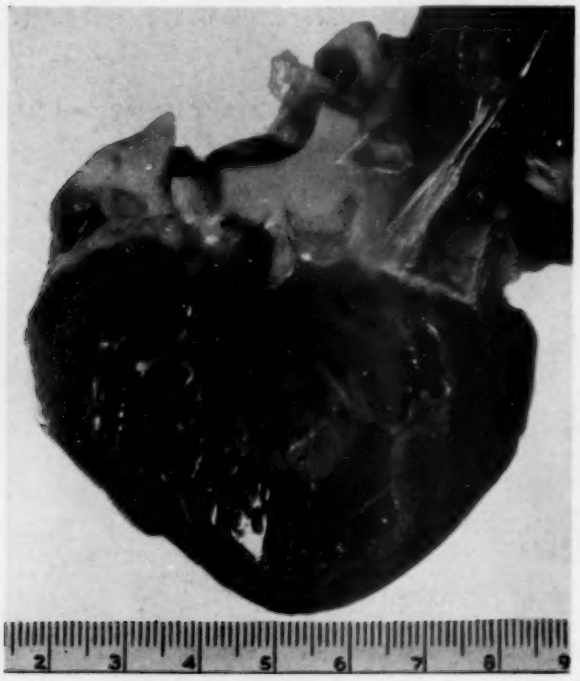

Fig. 4.—Heart of dog 7. Both the anterior and the posterior artery to the septum were ligated. The contrast between the pale region of infarction and the darker normal myocardium is clear (unfixed specimen). The corresponding electrocardiograms are shown in figures 5 *D* and *E*.

infarction followed, but electrocardiograms made several days after the second ligation failed to show any evidence of conduction disturbance (fig. 5 *C* and *E*). The resistance of the bundle of His and its branches to anoxemia, whether produced by coronary occlusion or by experiments with excised Purkinje fibers in vitro [8] is well known. But it seems

8. Pick, E. P.: Klin. Wchnschr. **3**:662, 1924. Wachstein, M.: Ztschr. f. d. ges. exper. Med. **83**:491, 1932.

unreasonable thus to explain persistence of good function in these tissues after what must be as complete and lasting an ischemia as it is possible to bring about by ligation experiments. It may be that the specific tissue is nourished, at least in part, through the endocardium, but at present a satisfactory explanation of the results obtained in the last two dogs is lacking.

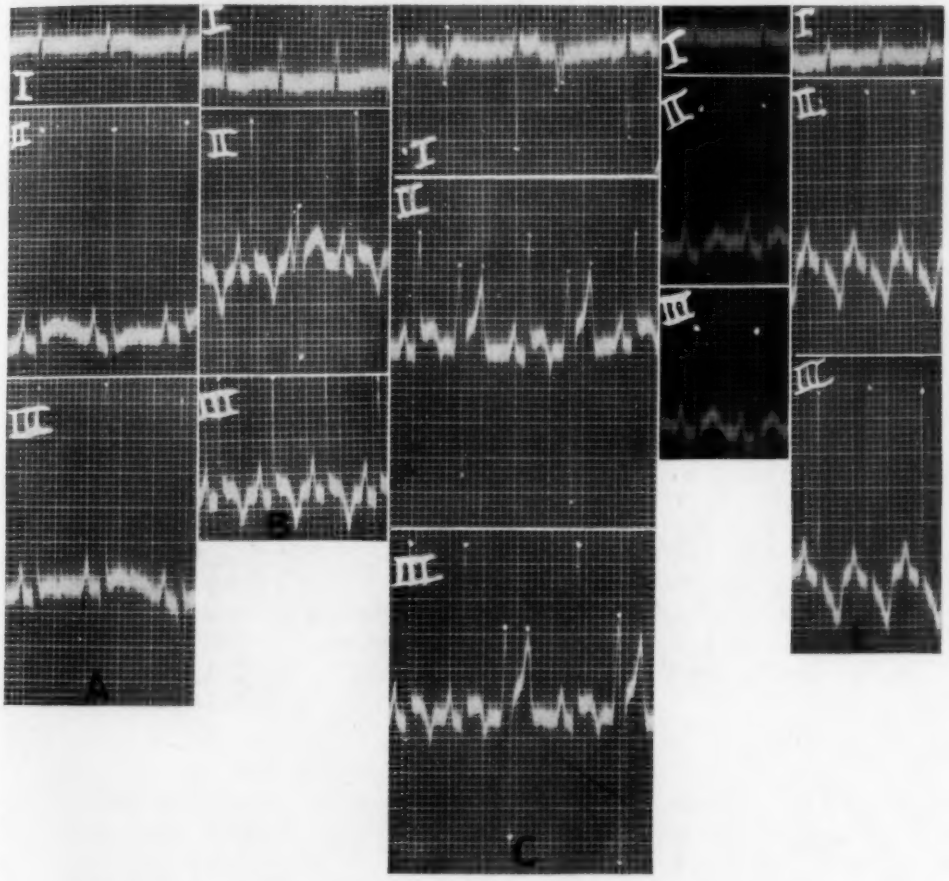

Fig. 5.—Electrocardiograms of dogs in which both the anterior and the posterior septal artery were ligated. Tachycardia, extrasystoles and elevation of the S T interval are the most noteworthy changes; there is no heart block. *A* is an electrocardiogram of dog 6, made thirty-three days after ligation of the anterior artery; *B*, an electrocardiogram of dog 6, made twenty-eight hours after ligation of the posterior artery; *G*, an electrocardiogram of dog 6, made three days after ligation of the posterior artery, showing coupled rhythm. *D*, an electrocardiogram of dog 7, made seven days after ligation of the posterior artery, which in this dog preceded ligation of the artery; *E*, an electrocardiogram of dog 7, made twelve days after ligation of the anterior artery.

SUMMARY

The sequences of ligation of the anterior septal artery in dogs have been previously reported. Ligation of the posterior septal artery also produced a characteristic infarct in the interventricular septum, with no more than transient alterations in atrioventricular conduction. In two animals, both the anterior and the posterior septal artery were ligated. The extensive infarction thus caused was also unaccompanied by lasting heart block.

RELATION BETWEEN BASOPHILIC INVASION OF THE NEUROHYPOPHYSIS AND HYPERTENSIVE DISORDERS

CHARLES SPARK, M.D.
NEW YORK

Recently Cushing [1] has advanced the theory that hypertensive states, such as eclampsia gravidarum and essential hypertension, are due to a hyperactivation of the neurohypophysis by a massive infiltration of the neural lobe by basophilic elements from the pars intermedia. A pressor substance elaborated by the basophilic cells becomes visible in the form of "hyaline bodies," which then become transformed into a fluid product. The latter makes its way through the neural tissue and infundibular stalk into the third ventricle and the hypothalamic region where, presumably, vasomotor centers are located. This hypothesis is based on the assumption that vascular tension is normally regulated, at least in part, by a mild degree of activity of the posterior lobe. Hypertensive disorders are due, therefore, merely to a pathologic exaggeration of a physiologic process.

While several investigators have assumed that the hormones extractable from the posterior lobe may be elaborated by the basophilic cells which are present in the region of the pars intermedia or in the nerve tissue itself, there are no reports in the literature concerning the possible relationship between this invading epithelial tissue and disturbances of vascular tension. The apparent disregard of what appears to be a morphologic indicator of an important physiologic activity will be understood after the subject has been reviewed.

REVIEW OF THE LITERATURE

Thom [2] appears to have been the first to report on basophilic invasion of the posterior lobe of the hypophysis in man. In 1901 he studied a small series of glands, and in the hypophysis of a woman 90 years old, who died of "senile marasmus," he observed that "the posterior lobe contains on one side numerous cyanophile cells which resemble and are connected with the epithelium of the anterior lobe, mimicking a sarcoma." He stated that such emigration of anterior lobe elements occurred chiefly in old age, and that a large part of the anterior portion of the posterior lobe might be occupied by anterior lobe cells.

In 1903 Erdheim [3] reported on a series of 50 hypophyses ranging from that of a fetus 24 cm. in length to that of a person 79 years of age. In 3

From the Laboratory Division, Montefiore Hospital.

1. Cushing, H.: Am. J. Path. **10**:145, 1934.
2. Thom, W.: Arch. f. mikr. Anat. u. Entwcklngsgesch. **57**:632, 1901.
3. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.

hypophyses from persons 50, 53 and 73 years of age (sex not stated), there was fairly marked infiltration of the posterior lobe by glandular elements.

In a study of hypophyseal adenomas, in 1907, Löwenstein [4] noted invasion of the posterior lobe. A case is illustrated in which the inwandering basophils broke through the capsule and infiltrated the surrounding fat tissue. On the basis of this observation he thought that basophilic infiltration of the posterior lobe might supply the foundation for large malignant adenomas.

In 1909, in their monograph on the changes in the hypophysis during pregnancy, Erdheim and Stumme [5] reported on invasion of the posterior lobe. Their control series of 25 persons was drawn predominantly from the younger age groups. It was made up of 12 females, half of whom were younger than 30 and none of whom was older than 49, and 13 males, 4 under 30 and 4 older than 50. Among these persons, a 37 year old woman and a 43 year old man, both with nephritis, and a 57 year old man with carcinoma of the gallbladder showed heavy invasion of the posterior lobe. If the persons under 30 are eliminated, since they are not expected to show this phenomenon, 2 of 9 males, or 22.2 per cent, and 1 of 6 females, or 16.6 per cent, exhibited it. From these observations one can be sure that Erdheim and Stumme had been looking for basophilic invasion in their cases of eclampsia. They described 12 cases of eclampsia in primiparas, all but 1 of whom were under 30 years of age. The age distribution was as follows: 16 (2), 18, 19, 20, 21, 22 (2), 26 (2), 29 and 32. Basophilic invasion was not observed in any of these cases. There were also 6 cases of eclampsia among multiparas, 1 of whom was of unknown age. The ages were as follows: 22, 23 (2), 32 and 37. In this group, also, basophilic invasion of the posterior lobe was not observed. While it is true that very mild degrees of invasion of the posterior lobe might have escaped observation, massive infiltration could not have been missed even though only one or two levels of the gland had been studied.

Lucien [6] in 1909 argued that invasion of the posterior lobe should not be classified with the adenomas since it was observed so frequently and was so variable. As a result of the examination of a large number of human hypophyses obtained at autopsies on persons dying of a large variety of diseases, Lucien concluded that these pseudo-adenomatous formations were encountered particularly in persons with certain chronic conditions of long standing and in the majority of aged persons. Lucien gave no details of his cases.

Kohn [7] in 1910 noted that basophilic infiltration of the posterior lobe occurred in childhood and in middle age, as well as in later life, when it was most commonly observed.

In 1911 Stumpf [8] observed that occasionally the inwandering cells were acidophilic. He believed that the invading glandular elements disintegrated sooner or later, and that the invasion increased with age. He thought that the pigment in the posterior lobe was derived from substances freed by the breakdown of these epithelial elements.

Nothdurft [9] in 1912 described a case of invasion of the posterior lobe under the title "Ein Fall von basophilem Adenom in der Neurohypophyse." From his

4. Löwenstein, C.: Virchows Arch. f. path. Anat. **188**:44, 1907.

5. Erdheim, J., and Stumme, E.: Beitr. z. path. Anat. u. z. allg. Path. **46**: 1, 1909.

6. Lucien, M.: Compt. rend. Soc. de biol. **67**:743, 1909.

7. Kohn, A.: Arch. f. mikr. Anat. u. Entwcklngsgesch. **75**:337, 1910.

8. Stumpf: Virchows Arch. f. path. Anat. **206**:70, 1911.

9. Nothdurft, K.: Frankfurt. Ztschr. f. Path. **10**:91, 1912.

illustrations it is clear that he was dealing with a basophilic infiltration of moderate degree. The case was that of a 50 year old man with a large meningioma compressing the right frontal, temporal and parietal lobes. There was no record of a blood pressure reading, but the retinal vessels were described as normal. There was no cardiac hypertrophy, but the kidneys were described as "atrophic with residua of nephritis." A microscopic examination of the kidneys was not made. Clinically, the case had been considered as one of cerebral arteriosclerosis with mental deterioration. It is interesting to note that Northdurft believed he might have been dealing with a basophilic adenoma of the posterior lobe, analogous to the basophilic adenomas which Erdheim [10] had reported in the anterior lobe in 1910, which Kraus [11] observed in 1914, which Brauchli [12] later noted in 1925 and which have been recently observed by Costello.[13]

In 1912 Tölken [14] examined 105 human hypophyses and came to the conclusion that the glandular elements in the posterior lobe were not anterior lobe cells but were derived from transformed embryonal cells of the cysts and cleft of the pars intermedia. Fifty hypophyses of his series showed chromophil invasion, but almost half showed only a slight degree. The distribution of the cases of basophilia according to age is shown in table 1. There it may be noted that 66 per cent of the cases of invasion of the posterior lobe occurred in persons past

TABLE 1.—*Incidence of Basophilic Invasion of the Posterior Lobe of the Hypophysis at Different Ages in Tölken's Series*

Age	Cases
0 to 20 years	1
20 to 30 years	6
30 to 40 years	9
40 to 50 years	1
50 to 60 years	6
60 to 70 years	13
Over 70 years	14

the age of 50 and only 14 per cent in persons under 30. The youngest person was 18 years old, a patient with phthisis. In another patient with phthisis, 22 years old, the invasion was marked. Tölken found no difference in degree of invasion due to sex or any particular disease. In 2 instances the invasion was by eosinophilic elements.

Goldzieher [15] reported the anatomic observations in 2 cases of diabetes insipidus. In that of a 34 year old man, numerous cysts occupied about half of the posterior lobe. The neural tissue adjacent to the cysts was replaced by fibrous connective tissue. There was also a marked growth of basophils in the posterior lobe and infundibulum. This observation is of interest in view of the assertion that the basophils produce an antidiuretic hormone.

In a study of the pigment in the posterior lobe of the human hypophysis, Vogel [16] discussed the problem of basophilic invasion of the pars nervosa. In his

10. Erdheim, J.: Frankfurt. Ztschr. f. Path. **4**:70, 1910.
11. Kraus, E. J.: Beitr. z. path. Anat. u. z. allg. Path. **58**:159, 1914.
12. Brauchli, N.: Frankfurt. Ztschr. f. Path. **31**:459, 1925.
13. Costello, R. T.: Proc. Staff Meet., Mayo Clin. **9**:177, 1934.
14. Tölken, R.: Mitt. a. d. Grenzgeb d. Med. u. Chir. **24**:633, 1912.
15. Goldzieher, M.: Verhandl. d. deutsch. path. Gesellsch. **16**:281, 1913.
16. Vogel, M.: Frankfurt. Ztschr. f. Path. **11**:166, 1912.

large series he found an unusually high proportion of hypophyses which exhibited this phenomenon. Since he gave no illustrations it is difficult to evaluate his descriptive terms. In fact, he criticized Tölken for having found basophilic invasion of the pars nervosa in only 50 of 105 hypophyses, and stated that had the latter studied his glands in serial section, the incidence of basophilic invasion would have been much higher. While it is true that mild degrees of invasion may be overlooked if only a few sections are studied, massive infiltration can hardly be missed. In a baby 9 months old, a girl, Vogel found the first evidence of emigration; "a few basophiles" were observed in the pars nervosa. It is remarkable that in a group of 18 infants and children he observed moderate infiltration in an 11 year old boy and marked invasion in 3 girls, 10, 15 and 16 years old. Vogel gave data on 45 males and 39 females, but 13 of the former and 6 of the

TABLE 2.—*Age Grouping of Vogel's Series of Persons with Basophilic Invasion of the Neurohypophysis*

Age, Years	Males	Females
21 to 25	8	4
26 to 35	4	8
36 to 50	9	11
51 to 65	7	6
66 to 83	4	4

TABLE 3.—*Grouping of Vogel's Series According to the Degree of Basophilic Invasion*

Degree of Infiltration	Males	Females	Percentage of Males	Percentage of Females
None	3	2	9.3	6.0
Very slight	0	3	0.0	9.0
Slight	4	5	12.5	15.1
Moderate	5	7	15.4	21.3
Marked	15	12	46.8	36.3
Extreme	5	4	15.4	12.1

latter have to be excluded because I am unable to interpret his descriptions unequivocally. The age groups are indicated in table 2.

Table 3 shows the groupings of Vogel's series according to the degree of basophilic invasion. There is shown a slight tendency for the more marked invasions to occur oftener in males. It is of interest to note that a 30 year old woman who died two weeks post partum with a diagnosis of "kidney of pregnancy" had marked infiltration, and that a 37 year old eclamptic woman had very marked infiltration, as did a 64 year old woman with contracted kidneys. However, similar degrees of invasion were noted in persons with nonhypertensive diseases. It is difficult to understand why only Vogel should have observed such marked degrees of invasion in young subjects; 6 males and 2 females under 30 years of age in his series showed marked or very marked invasion. He stated that sex and disease had no influence on the process.

In discussing the age changes of the hypophysis, Aschoff [17] mentioned that after birth the most profound changes occurred in the pars intermedia. Here, the epithelial-lined cystic spaces divided into numerous small colloid-filled vesicles.

17. Aschoff, L.: München. med. Wchnschr. **60**:782, 1913.

The epithelium of these vesicles transformed from undifferentiated cells into basophils which, beginning with puberty, sometimes earlier, wandered into the posterior lobe. This emigration lasted throughout life and disappeared gradually in old age. It showed marked individual variations. Aschoff stated that at that time several investigators had advanced the hypothesis that through the transformation and disintegration of these basophilic cells there were released substances within the posterior lobe on which part of its pharmacologic action depended.

In 1920 Kraus [18] described the changes in the hypophysis in 23 cases of diabetes mellitus. The histology of the posterior lobe was mentioned specifically in all instances. While no readings of blood pressure were given, it was stated that 3 patients had hypertrophy of the left ventricle without evidence of valvular disease or nephritis, and therefore they probably had essential hypertension as well. The observations on the posterior lobe can be summarized as follows:

In the group between the ages of 14 and 35, 1 female showed no invasion, 2 very slight and 1 slight invasion. One male showed very slight and 3 slight infiltration. In the group between the ages of 36 and 49, 2 women and 1 man showed no invasion while 2 men showed very slight infiltration. Significant degrees of invasion occurred during the age period from 59 to 77 years. Two women and 1 man showed no invasion. Slight invasion was exhibited by 2 men. Three men and 1 woman showed moderate degrees of infiltration and 1 man showed marked invasion. The series is too small to allow one to draw conclusions regarding the relation to sex or blood pressure. Of the 3 men showing left ventricular hypertrophy, 1 showed slight and 2 moderate degrees of invasion. In summary, then, the older persons showed the average percentage of basophilic invasion. Four of 15 persons over 35 years of age showed moderate and 1 marked infiltration. More extensive basophilic infiltration was noted in a group of 8 nondiabetic patients, all males. Five persons ranging in age from 34 to 59 years showed marked infiltration. The diagnoses in their cases were: Addison's disease, dementia paralytica, neuroma of the spinal cord, purulent peritonitis and hemorrhagic pancreatitis, respectively. Two of this group showed slight and 1 very slight infiltration.

Plaut [19] in 1922 maintained that the marked irregularity of basophilic invasion argued against its having a normal function. In general, the ingrowth was proportionate to age.

Höppli,[20] in a study of the basophils in the anterior lobe and their relation to renal diseases, examined 45 glands and mentioned the observations in the posterior lobe in all but a few cases. In his opinion, the invading basophils came from the anterior lobe and were derived from the basophils in the adenohypophysis. He hesitated in drawing conclusions regarding the function of these inwandering cells, but asked whether they might not have something to do with the transport of secretion.

Table 4 summarizes the grouping of Höppli's patients with renal disease according to the degree of invasion of the posterior lobe. The marked preponderance of males in the groups showing the higher degrees of infiltration of the neurohypophysis is undoubtedly due in part to the fact that only 7 females out of the total of 15 were past the age of 50. However, if persons 35 years old or under only are considered, one observes the distribution shown in table 5.

18. Kraus, E. J.: Virchows Arch. f. path. Anat. **228**:68, 1920.
19. Plaut, A.: Klin. Wchnschr. **1**:1557, 1922.
20. Höppli, R.: Frankfurt. Ztschr. f. Path. **26**:22, 1922.

The distribution of the younger males in the groups with higher degrees of infiltration is noteworthy. Of the 12 persons (all males) who showed moderate to marked basophilic infiltration, 4 had renal amyloidosis; for 3 of these the readings of the systolic blood pressure were recorded (the readings varied from 90 to 120 mm. of mercury). There were 4 persons with chronic glomerulonephritis; 3 of these had hypertension and all had cardiac hypertrophy. Three persons with primary contracted kidney were included in the group; incomplete data were offered on 1; the remaining 2 patients had normal blood pressure and no cardiac hypertrophy. The twelfth patient had hydronephrotic contracted kidneys with a possible glomerulonephritis, marked cardiac hypertrophy and a systolic blood pressure of over 200.

On the other hand, Höppli recorded 17 cases of hypertensive diseases with slight or no basophilic invasion. Of these, 6 were instances of essential hyper-

TABLE 4.—*Grouping of Höppli's Patients with Renal Disease According to the Degree of Basophilic Infiltration of the Posterior Lobe*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
None	10	5	35.7	37.0	33.3
Very slight	0	1	2.3	0	6.6
Slight	5	9	33.3	18.4	60.0
Moderate	3	0	7.1	11.1	0
Marked	9	0	21.4	33.3	0

TABLE 5.—*Grouping of Höppli's Patients Under 35 Years of Age with Respect to the Degree of Basophilic Invasion of the Posterior Lobe*

Degree of Infiltration	Males	Females
None	1	2
Very slight	0	1
Slight	3	5
Moderate	2	0
Marked	2	0

tension, 9 of chronic glomerulonephritis, 1 of acute glomerulonephritis and 1 of cystic kidneys.

If only the 13 patients with primary contracted kidney are considered, it is noted that 8 showed no basophilic invasion, 2 slight and 3 marked infiltration. For 6 of the 13 patients, high blood pressure readings were recorded, and of these, 2 showed slight and 4 no basophilic infiltrations. Three patients had hypertrophy of the left ventricle, and for 2 of these no blood pressure readings were recorded. The systolic reading for the third was 135 mm. of mercury when the patient was dying. In all 3 patients the posterior lobe was free from basophils. The marked degrees of infiltration occurred in 2 patients with normal systolic pressures and no cardiac hypertrophy and in a third on whom there were no clinical or anatomic data regarding the size of the heart. It is possible that the latter cases were not instances of essential hypertension, but merely of arteriosclerotic contracted kidneys. Still, the absence of basophilic infiltration in the patients showing raised blood pressure is significant.

Höppli mentioned the observations in the posterior lobe in 3 women whose condition was diagnosed as eclampsia: A 34 year old woman had a systolic

reading that varied from 90 to 220 mm. of mercury, and another, 32 years old, had a "fluctuating blood pressure." These showed only slight basophilic invasion. The third woman, 29 years old, with normal blood pressure, showed very slight infiltration.

Dieckman [21] examined 31 hypophyses from stillborn infants and others up to 1 year of age and 41 glands from patients from 1 to 70 years of age. He found heterotopic epithelial elements in 74 per cent of the first group and in only 39 per cent of the older group. He insisted that with serial sectioning of glands from even the youngest subjects these heterotopic cells would be found almost constantly. He dissented from the emigration theory of other writers, and claimed that these epithelial elements were misplaced during embryonal development. However, he did not attempt to explain the massive infiltration that one not infrequently encounters in older subjects, and he was ambiguous in his description of glandular structures in the posterior lobe.

In a study of the development of the human endocrine organs, Cooper [22] mentioned that basophils in the pars intermedia increased with age and were most numerous in adult life. No details were given to support this contention.

TABLE 6.—*Grouping of Kiyono's Series with Basophilic Invasion of the Posterior Lobe of the Hypophysis According to Age*

Age, Years	Males	Females
16 to 35	6	3
36 to 50	7	8
51 to 60	7	6
61 to 72	1	6

In 1926 Schönig [23] carefully examined 67 human hypophyses and found marked basophilic invasion in 19. He found it in 11 of the 33 hypophyses from males. He found more marked invasion in persons who had met with accidental death than in those who had died of long illnesses, and stated also that the invasion was most marked in older people. In his opinion, the invading elements were derived from the pars intermedia.

In a thorough monograph on the histopathology of the hypophysis, Kiyono [24] gave detailed protocols of 47 cases. In 2 cases the ages of the subjects were not included, and in a third case the histology of the gland was so altered by tumor infiltration that no estimate of the preexisting structure could be made. Hence there remain 44 cases suitable for statistical analysis. He described the degree of invasion of the posterior lobe in terms that convey a clear idea as to his observations. The age distribution of the patients showing basophils in the posterior lobe is shown in table 6.

Table 7 shows the distribution according to the degree of basophilia. It is clearly shown in the table that the heavy and moderate infiltrations occur preponderantly in the males, and this is all the more remarkable when one considers the fact that the males are, on the average, younger than the females. Of the 7 males who showed moderate to marked infiltration, 2 were 50 and 3 below 50

21. Dieckman, D.: Virchows Arch. f. path. Anat. **252**:113, 1924.

22. Cooper, E. R. A.: The Histology of the More Important Human Endocrine Organs at Various Ages, New York, Oxford University Press, 1925.

23. Schönig, A.: Frankfurt. Ztschr. f. Path. **34**:482, 1926.

24. Kiyono, A.: Virchows Arch. f. path. Anat. **259**:388, 1926.

years of age, while the 3 females with a similar degree of infiltration were over 50 years of age. There were 5 persons who, from the anatomic findings, probably had essential hypertension. Of these, 1 showed heavy basophilic invasion, 1 slight invasion and 3 none. Kiyono was cognizant of a sex difference in the invasion of the posterior lobe, and attempted to explain the preponderance of more marked infiltration in males on the basis of a more marked cyst formation in the region of the pars intermedia in these subjects.

Lewis and Lee [25] studied in serial section 30 human hypophyses from persons ranging in age from new-born to 73 years. They observed that basophilic cells were present in the posterior lobe at all ages but became more numerous and infiltrated the neural tissue progressively with increasing age. Occasionally eosinophilic cells were found in the juxtaglandular portion of the posterior lobe.

According to Guizzetti,[26] the invading basophils infiltrated the pars nervosa in four places; two midway between the caudal and cephalic extremities, one on either side of the midline, and two at the caudal end of the neural lobe. He could find no relation between the degree of basophilic infiltration and the physiologic sexual state (e. g., pregnancy) or any particular malady. Age seemed to be the only factor which influenced this invasion. He found it in one

TABLE 7.—*Distribution of Kiyono's Series with Respect to the Degree of Basophilic Invasion of the Neurohypophysis*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
None	9	15	54.5	42.8	65.2
Slight	5	5	22.7	23.8	21.7
Moderate	3	2	11.3	14.2	8.6
Marked	4	1	11.3	19.0	4.3

third of the group between 10 and 20, two thirds of that between 20 and 30, and four fifths of the group between 30 and 85. The degree of invasion was not mentioned in any case.

Berblinger,[27] in a criticism of Schönig, denied the presence of a pars intermedia analogous to that of lower animals. He found eosinophils as well as fully ripened, vacuolated basophils in the posterior lobe. In his opinion, the posterior lobe was invaded by basophils from the anterior lobe rather than from the pars intermedia.

Rasmussen [28] made a volumetric analysis of 111 hypophyses from normal males ranging in age from 20 to 76 years, and found that the epithelium of the pars intermedia, but not the colloid, gradually increased with age. Under epithelium of pars intermedia he included three types of cells: the cuboid or low columnar cells forming a more or less imperfect layer between the pars anterior or the cleft and pars nervosa; the cuboid or flattened cells which enclose the colloid masses that are outside the cleft, and the basophilic cells scattered in the neural tissue itself. This increase in volume is largely due to an accumulation of basophilic cells. He published a photomicrograph of the hypophysis of a normal adult male showing a moderate degree of basophilic infiltration of the posterior

25. Lewis, D., and Lee, F. C.: Bull. Johns Hopkins Hosp. **41**:241, 1927.
26. Guizzetti, P.: Sperimentale, Arch. di biol. **81**:583, 1927.
27. Berblinger, W.: Frankfurt. Ztschr. f. Path. **35**:497, 1927.
28. Rasmussen, A. T.: Endocrinology **12**:129, 1928.

lobe and stated that it represented the maximum development of the pars intermedia in his series. Rasmussen also could find no correlation between the amount of epithelium and the amount of colloid in the region of the pars intermedia.

Lucien [29] advanced the idea that the changes in the hypophysis of the aged person may be due to a general slowing up of secretory function and a marked reduction of excretory function. According to his hypothesis, the accumulation of basophilic cells in the pars nervosa is due to a slowing down of the normal cellulytic processes and therefore represents an actual diminution in secretory function. In this way he explained the accumulation of colloid and basophils in the posterior lobe of the hypophysis of the aged person. However, the occurrence of basophilic invasion in the third and fourth decades and its frequent absence in extreme old age render this interpretation improbable.

In studying the origin of the basophilic cells of the posterior lobe of the human hypophysis, Rasmussen [30] concluded that the undeveloped cells of the pars intermedia, both in the stratum which forms the posterior wall of the cleft and in the strands and tubules which grow backward from it, may become basophilic and infiltrate the nerve tissue. However, he did not deny the possibility of migration of cells from the anterior into the posterior lobe. This concept is similar to that expressed by Tölken in 1912 and by Aschoff in 1913.

Orlandi [31] carefully studied 352 human hypophyses and could find no relation between the morphologic characteristics of the invading basophils and any particular disease or constitutional type. In all of his 18 cases of primary and 10 cases of secondary contracted kidney he observed a rich basophilic infiltration of the neurohypophysis. However, in cases in which there was no anatomic evidence of hypertension there was exhibited a similar degree of invasion. As regards the influence of sex, he found that basophilic invasion was more frequent and more extensive among males. In females it occurred later and to a lesser degree.

Löffler [32] studied heterotopic cells in the posterior lobe and infundibulum and gave detailed protocols of 19 cases. In 7 cases, the presence or absence of basophils was specifically mentioned. Since the histologic observations in the neurohypophysis were described in great detail, the lack of specific mention of basophils probably meant the absence of these elements. The cases were nearly all in the older age groups. There were 8 males ranging from 50 to 71 years, except 1 who was 29 years of age. There were 11 females varying from 48 to 83 years of age, with 5 in the eighth decade (70 to 80). Basophilic invasion was present in 4 of the series, namely, a 50 year old man with dementia paralytica ("very rich"), a 62 year old woman with uterine carcinoma ("moderate"), and 2 men 66 and 59 years old with senile dementia and dementia paralytica, respectively. In the latter 2 cases the degree of invasion was not mentioned. Thus, 3 of 8 men and only 1 of 11 women showed some degree of basophilic invasion. Its absence in a group of 8 women over 65 is unusual.

Bucy [33] proposed a mechanical theory to explain, at least in part, the presence of epithelial cells in the nerve tissue. His illustrations show clearly small fenestra-

29. Lucien, M.: Rev. franç. d'endocrinol. **6**:441, 1929.

30. Rasmussen, A. T.: Am. J. Anat. **46**:461, 1930.

31. Orlandi, N.: Arch. ital. di anat. e istol. pat. **1**:1, 1930.

32. Löffler, E.: Virchows Arch. f. path. Anat. **274**:326, 1930.

33. Bucy, P. C.: The Hypophysis Cerebri, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber Inc., 1932, vol. 2, p. 707.

tions in the connective tissue capsule between the anterior and the posterior lobe. These openings permit nerve fibers to pass into the region of the pars intermedia and epithelial cells to invade the pars nervosa. But this theory cannot explain the presence of basophilic cells deep within the nerve tissue in the presence of a colloid-filled cleft which extends along the entire surface of contact between the two lobes.

In 1933 Cushing [34] suggested that the morphologic observation of infiltrative basophilia of the pars nervosa was of fundamental physiologic importance. He regarded this cellular hyperactivity as an expression of functional hyperactivation of the posterior lobe, and believed that it represented the pathologic basis of hypertensive disorders. Cushing first observed this "cellular hyperactivation of the posterior lobe" in a case of basophilic adenoma of the pars anterior and later noticed the same phenomenon, but to a somewhat less degree, in a few cases of eclampsia and essential hypertension. Then in 1934, in a more extensive paper,[1] he described in detail several cases of eclampsia and essential hypertension. In this communication he went one step further and claimed that the degree of invasion of the posterior lobe was a measure of the neurohypophyseal activation. He thus stressed the quantitative aspects of this morphologic phenomenon. Cushing cited 9 cases of eclampsia of which only 6 were typical. In 2 typical cases, in obese subjects 38 and 44 years old, there had been hypertension for several years before the terminal episode, which was marked in both instances by absence of convulsions. In regard to the observations in the posterior lobe in cases of essential hypertension, Cushing stated that marked basophilic infiltration was common, but he presented no statistical data to support his contention. In a small series of cases the error of chance distribution cannot be eliminated. In his article, Cushing quoted several other authors with reference to the frequency of basophilic invasion of the posterior lobe in the absence of hypertension. Rasmussen stated that among 240 serially sectioned glands only 6 showed massive infiltration. The ages of the patients were not given. Southard and Canavan studied 100 glands from patients with mental disorders, the ages of whom ranged from 34 to 83 years of age, the average age being 50 years. Serial sections were not made. In 64 instances there was no infiltration; in 23 there was slight and in 13 marked invasion. Of 100 glands from Johns Hopkins Hospital (not cut serially), 62 showed no infiltration, 22 slight, 9 moderate and 7 heavy invasion. Cushing also mentioned that in 6 cases of eclampsia single sections supplied to him failed to show the presence of basophilic invasion in any instance. Berblinger [35] reported a case of eclampsia in a 34 year old primipara with convulsions, marked hypertension (180 systolic and 140 diastolic), oliguria, albuminuria (20 per cent) and edema. At autopsy there was noted a nonsuppurative hypophysitis involving the anterior lobe, but no basophils or cellular infiltrations in the pars nervosa.

In regard to the observations in the posterior lobe in the reported cases of basophilic adenoma of the pars distalis, Cushing [36] stated that "in single sections from the Parkes Weber case and one or two others, no notable basophilic invasion of the posterior lobe is seen." However, in the Raab-Kraus case a large adenomatous mass of basophils occupied three fourths of the posterior lobe. In

34. Cushing, H.: Am. J. Path. **9**:539, 1933.

35. Berblinger, W.: Centralbl. f. allg. Path. u. path. Anat. **44**:161, 1928.

36. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

the case of basophilic adenoma recently reported by Craig and Cran,[37] the hypophysis showed no abnormalities in the posterior lobe. The hypophysis in Teel's[38] case was sectioned serially, but basophilic invasion of the posterior lobe was not mentioned. The pituitary gland in the Mooser[39] case was described as normal in all its parts, but the type of examination was not stated. The photomicrographs of the gland in the cases reported by Anderson and Bauer, which Cushing[36] showed, failed to reveal any basophilic invasion of the posterior lobe. The hypophysis in the case reported by Bishop and Close[40] had a very large basophilic adenoma in the adenohypophysis; the posterior lobe was not described. However, one gets the impression from the photomicrograph (taken under a magnification of very low power) that there are no basophils in the nerve tissue. The blood pressure averaged 250 systolic and 180 diastolic, and the kidneys were contracted at autopsy.

Russell, Evans and Crooke[41] reported 2 cases of hypertension in which were presented certain features of pituitary basophilism. The first case was that of a man 31 years of age who died in uremia. A 6 mm. basophilic adenoma was present in the anterior lobe. The posterior lobe was small and contained few basophils. The kidneys showed chronic glomerulonephritis. The second case was that of a 33 year old woman who had generalized obesity of long standing and evidences of toxemia during all three pregnancies. She died four years after the last pregnancy, which had been terminated by a cesarean section. After the uterus had been emptied, the blood pressure fell only temporarily. There was a moderate hypertrichosis but no amenorrhea. Death was due to a cerebral hemorrhage. In the anterior lobe there was a small basophilic adenoma, 1.5 by 1.2 by 2 mm. There was only a small group of basophils in the posterior lobe. The kidneys showed benign nephrosclerosis.

Zeynek[42] recently studied in detail the hypophyses from 32 persons with constitutional obesity, of whom only 7 were males. No blood pressure readings were recorded, but in 5 instances there was cardiac hypertrophy in the absence of valvular disease. While it is true that hypertension is relatively common in such a group, only a small percentage would not show some degree of cardiac hypertrophy at autopsy. Four women and 1 man, all in the prime of life (from 47 to 55 years), showed some degree of cardiac hypertrophy. All showed extensive basophilic infiltration of the pars nervosa. Of the remaining 27 persons, 11 females, of whom only 3 were under 50 years of age, showed no or very slight basophilic invasion. However, 5 of 6 males, of whom 3 were younger than 50 years, exhibited extensive epithelial invasion, and the remaining male showed few basophils in the nerve tissue. Ten females, of whom 2 were below 40 years of age, showed abundant infiltration.

Even in this small series one is struck by the high percentage of basophilic infiltration of the posterior lobe. One 61 year old woman showed a 4 by 2 mm. adenomatoid mass of basophils occupying half the posterior lobe. Even though all those who presumably had essential hypertension showed basophilia of the posterior lobe, the number is too small to allow one to draw conclusions. About 80 per cent of these obese persons showed a significant increase of basophils in

37. Craig, J., and Cran, B.: Quart. J. Med. **27**:57, 1934.
38. Teel, H. M.: Arch. Neurol. & Psychiat. **26**:593, 1931.
39. Mooser, H.: Virchows Arch. f. path. Anat. **229**:247, 1921.
40. Bishop, P. M. F., and Close, H. G.: Guy's Hosp. Rep. **82**:143, 1932.
41. Russell, D. S.; Evans, H., and Crooke, A. C.: Lancet **2**:240, 1934.
42. Zeynek, E.: Frankfurt. Ztschr. f. Path. **44**:387, 1933.

the anterior lobe, and in 1 woman, 32 years old, there was a large, poorly circumscribed nodule of basophils in the anterior lobe, adjacent to the posterior lobe and invading the latter. One is tempted to bring basophilic increase in the anterior or the posterior lobe into some relation with fat metabolism, but it is difficult to state whether the increase is primary or secondary to the metabolic disturbance.

MATERIALS AND METHODS

This study includes material that has come to the laboratory to be sectioned within the past two years, as well as material from autopsies as far back as 1915. The greater part, however, was studied clinically and anatomically during the past

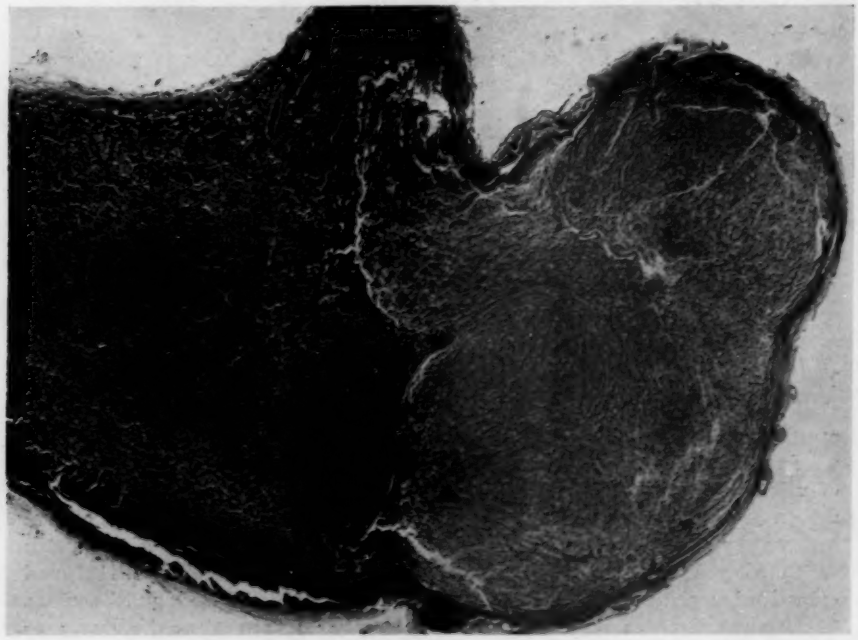

Fig. 1.—Basophilic infiltration of the type classified as group 2; × 16. Only a few scattered basophils are present in the lower part of the pars nervosa. This case was observed in the hypophysis of a 50 year old woman with essential hypertension. Her blood pressure was from 208 to 242 systolic and from 135 to 160 diastolic.

In all the figures the glands are sectioned sagittally, and in figures 1 to 6 the dorsum faces the top of the page.

five years. In selecting control glands, the younger age groups were largely avoided in order to establish a group of approximately the same ages as the hypertensive group. Only those were selected who had had at least one reading of blood pressure, the majority having had repeated estimations.

The glands were fixed in either Orth's or Helly's fluid. Most of them were cut sagittally into as many thin slivers as possible (from four to seven), embedded in paraffin, sectioned 6 microns thick and stained with hematoxylin-eosin, hematoxylin followed by Mallory's connective tissue stain, and with aniline blue-

hematoxylin-Van Gieson stain.[43] Several ribbons of from eight to eighteen sections each were mounted from each block. Complete serial sections were not made since they are not necessary if different levels are studied in this way. A few glands were sectioned horizontally into equal parts, and both were embedded. In the cases in which autopsy was performed many years ago, only half the gland was available for study, so only two or three sections through both lobes were examined. Then, in 16 cases of hypertension and 8 of the control cases, only single sections through both lobes were available, because of the loss of the original tissue. However, any errors of technic are roughly equally distributed between the hypertensive and control groups.

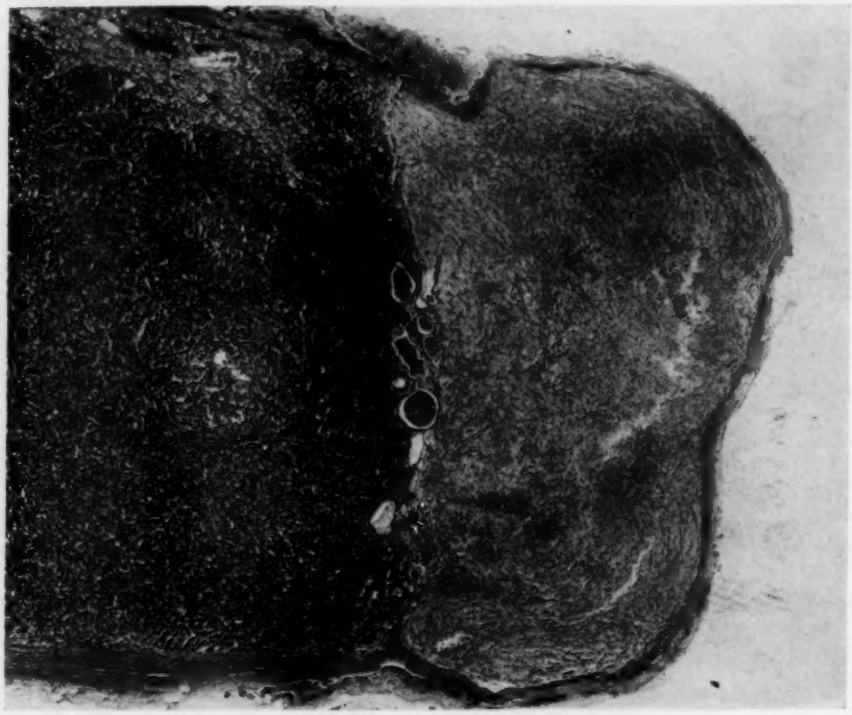

Fig. 2.—Basophilic infiltration in the lower portion of the posterior lobe (group 2); × 16. There is a minute chromophobe adenoma in the anterior lobe. This infiltration occurred in a 37 year old woman with rectal carcinoma. The blood pressure was 105 systolic and 75 diastolic.

Unfortunately a large number of preserved glands from hypertensive patients as well as from controls were made inaccessible to further histologic study because of maceration of the posterior lobe during removal, loss of the remaining gland tissue after removal of one sliver for routine sectioning, or misplacement of the entire gland. The glands from the older controls were removed from the jars of stored fixed tissue without any previous examination of the routine stained

43. Spark, C.: J. Lab. & Clin. Med. **20**:508, 1935.

sections of the same glands. The glands obtained at the autopsies during the previous eighteen months were selected in order, the only basis for elimination from the series being excessive postmortem change or damage to the posterior lobe during removal. A limited number of young persons were included in the control series in order to maintain age groups roughly comparable with those of the hypertensive patients.

DEGREES OF BASOPHILIC INFILTRATION

Since the quantitative aspects of basophilia of the posterior lobe had been stressed by Cushing, an attempt was made to grade the cases into

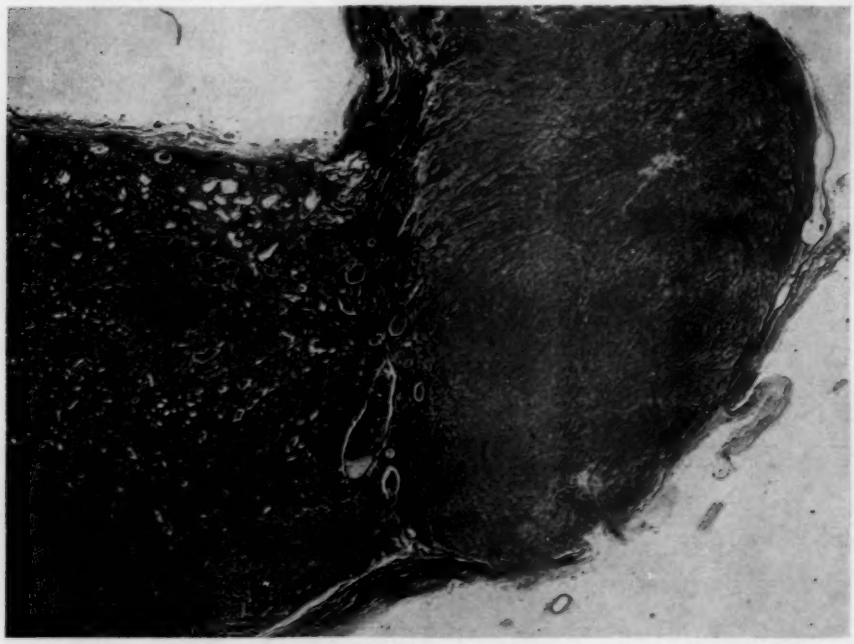

Fig. 3.—Basophilic infiltration representative of group 3; × 16. Included in this group are cases showing from two to three times the amount of invasion illustrated. This infiltration occurred in a 45 year old woman with cirrhosis of the liver. Her blood pressure was 96 systolic and 60 diastolic.

a few groups, which are necessarily poorly defined. Group 1 includes those cases in which there were no basophilic cells in the nerve tissue in any of the sections examined. It is obvious that the percentage of cases falling into this category would vary inversely with the number of sections examined. With complete serial sections I doubt whether any case would not show a few basophils in the juxtaglandular region of the pars nervosa. Figures 1 and 2 illustrate group 2, in which only a few isolated cells or a small group of cells were seen adjacent to the

region of the pars intermedia. In group 3 are cases in which there was a slight invasion by basophils (figure 3). This degree corresponds to that of the basophilia of the posterior lobe in Cushing's seventh case of eclampsia, illustrated on plate 64 of his article.[1] Figure 4 illustrates a moderate degree of invasion of the type seen in the cases placed in group 4. In group 5 are included all instances of marked infiltration, and figures 5 and 8 illustrate to what extent the neural lobe may be occupied by basophils. In the entire series there were 2 glands, both from nonhypertensive subjects, that showed a degree of epithelial infil-

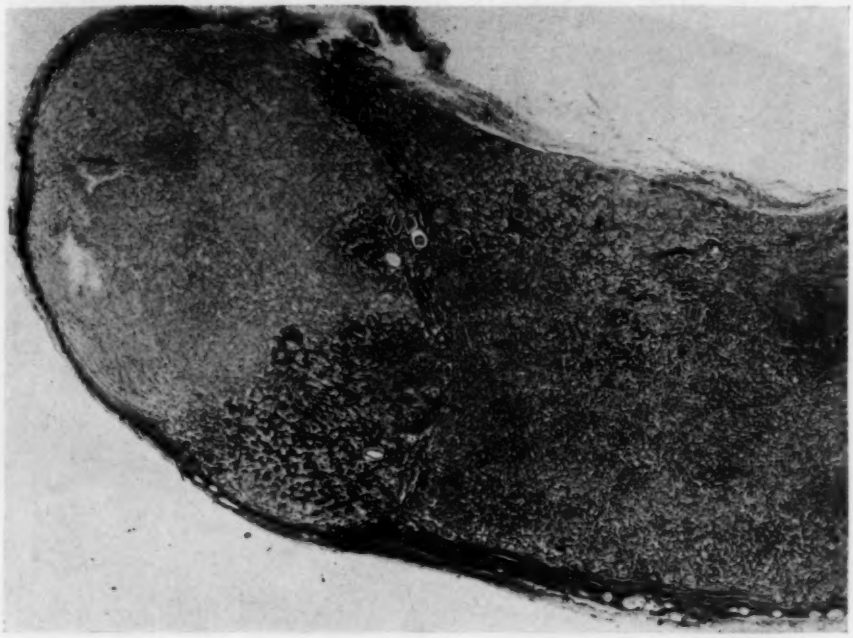

Fig. 4.—Basophilic infiltration representative of group 4; × 16. The invading basophils show a variable degree of granulation. The cells at the caudal end of the posterior lobe show the heaviest granulation. The arrow points to a small group of "large epithelial cells," which are probably of glial origin. This was observed in the hypophysis of a 60 year old woman with mammary carcinoma (case 28, table 19). Her blood pressure was 154 systolic and 88 diastolic.

tration which was much more extensive than that in any of the other cases. These were placed in group 6. Figure 7 illustrates one of these cases.

THE POSTERIOR LOBE IN ESSENTIAL HYPERTENSION

Seventy cases are included in this series. Only single sections through both lobes were available in 16 instances, leaving 54 cases in which from two to five levels of the posterior lobe were studied. The

Fig. 5.—Basophilic infiltration typical of group 5; × 16. The adenoma in the anterior lobe is of the chromophobe type. This infiltration was observed in a case of chronic lymphatic leukemia in a 59 year old man (case 11, table 20). His blood pressure was 140 systolic and 80 diastolic.

Fig. 6.—Basophilic infiltration (group 5); × 14. The arrows demarcate the two lobes. There are also within the nerve tissue many small polygonal cells without specific granules (arrows). The degree of infiltration is somewhat greater than that shown in figure 5. This invasion occurred in a 73 year old man with essential hypertension (case 8, table 20). His blood pressure was from 134 to 180 systolic and from 88 to 95 diastolic.

age and sex distribution of the hypertensive group is shown in table 8. It is evident that the women were, on the average, slightly younger than the men.

A separation of cases of essential hypertension into different groups depending on height of blood pressure, state of renal function, degree of cardiac hypertrophy, eyeground changes and clinical course might have some value in a series of several hundred cases, but in a group of only 70 cases such a procedure might lead only to error. Suffice it to

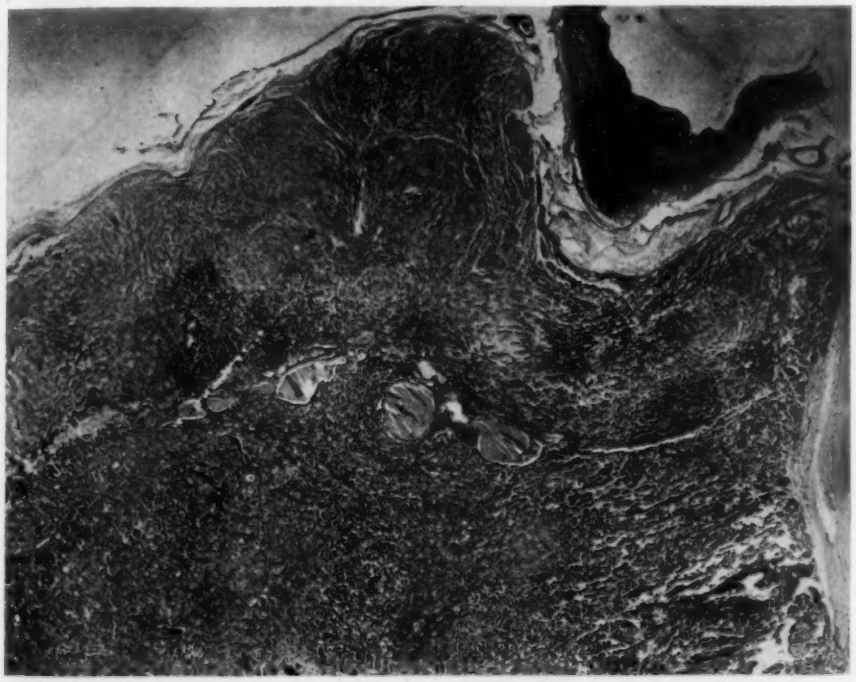

Fig. 7.—An extensive degree of basophilic infiltration (group 6). The magnification was reduced to × 12 in order to include most of the posterior lobe. The hypophysis was the size of a cherry, owing largely to enlargement of the anterior lobe. There were numerous adenomatoid nodules of basophils in the pars anterior. The acidophils, while absolutely increased, were relatively less numerous than the basophils. At another sagittal level in the posterior lobe there was a 4 by 2 mm. mass of closely packed basophils. This was observed in the hypophysis of an 80 year old obese woman who had a meningioma of the spinal dura (case 16, table 20). Her blood pressure was from 128 to 150 systolic and from 78 to 80 diastolic.

say that only unquestionable cases of essential hypertension are included in this series. In some of the cases the clinical course was fairly rapid, and the condition was diagnosed clinically as malignant hypertension, while in other cases the progress was protracted and mild. In none of the cases, however, were the necrotizing renal lesions of so-called malig-

nant nephrosclerosis shown. Cases of glomerulonephritis were excluded by histologic examination of the kidneys. The marked variation in diastolic, as well as in systolic, blood pressure is well known, and has been emphasized by Ayman.[44] Still it may be worth while to record that in half the cases the systolic reading hovered around 200 mm. of mercury or over, while in the remaining cases it varied widely between 140 and 200 mm. In 34 cases the diastolic pressure averaged 110 mm. of mercury or higher, while in the other instances it fluctuated between 90 and 110 mm.

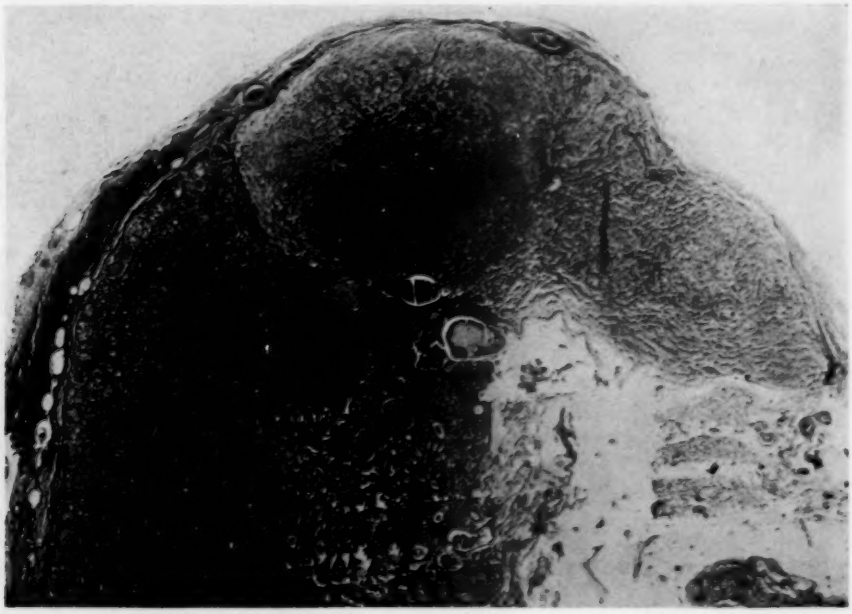

Fig. 8.—Basophilic invasion (group 5); × 16. An adenomatoid mass of basophils may be seen in the posterior lobe. The gland is flattened dorsoventrally. This was from a 72 year old woman with diabetes mellitus who presented evidence of antecedent hypertension (case 10, table 20). Her blood pressure was 120 systolic and 68 diastolic.

Table 9 shows the grouping of the hypertensive patients according to the degree of basophilic infiltration of the pars nervosa. From this table it is clear that the male hypertensive group showed moderate to marked basophilic infiltration more than twice as frequently as the female group. This may have been due in part to the preponderance of younger females.

Table 10 shows the grouping of the 57 hypertensive patients who were over 50 years of age. Apparently, when the factor of age is elim-

44. Ayman, D.: Arch. Int. Med. **48**: 89, 1931.

inated, there is a definite but slightly less striking difference between the male and the female hypertensive groups. However, a much larger series of cases will have to be studied before any valid conclusions can be drawn.

One may raise the objection that by including the cases in which only single sections through both lobes were studied the percentage of

TABLE 8.—*Grouping of Hypertensive Patients with Respect to Age and Sex*

Age, Years	Males	Females
24 to 35	2*	0
36 to 50	2	9
51 to 65	20	16
66 to 84	11	10

* This group included a 24 year old man with severe, persistent hypertension, marked albuminuria, vascular neuroretinitis, slight nephrosclerosis and cortical suprarenal adenomas. The case was reported by Oppenheimer and Fishberg (Arch. Int. Med. **34**: 631, 1924) as one of hypertension due to multiple tumors of the suprarenal cortex.

TABLE 9.—*Grouping of the Hypertensive Series According to the Degree of Basophilia of the Pars Nervosa*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
1	3	7	14.2	8.5	20.0
2	5*	12	22.8	11.4	34.2
3	12	10	34.2	40.0	28.5
4	10	3	17.1	25.7	8.5
5	5	3	11.4	14.2	8.5

* This includes the patient 24 years old. The gland was sectioned sagittally at three levels.

TABLE 10.—*Grouping of Fifty-Seven Hypertensive Patients Who Were Over 50 Years of Age*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
1	3	7	66.6	58.0	76.8
2	3	8			
3	12	5			
4	8	3	33.3	41.9	23.0
5	5	3			

cases in the higher groups might be reduced. Table 11 shows the distribution of the 54 cases in which there was examination of more than one section through both lobes. The error due to the inclusion of cases with single sections is shown to be insignificant. There are only 3.4 per cent more cases in groups 4 and 5 when the cases with single sections are eliminated.

As has been mentioned, there is no sharp line of distinction between any types of essential hypertension. While undoubtedly some cases have

in common a relatively rapid course, marked fundus changes, renal impairment and a highly elevated tension, and other cases are characterized by only moderate hypertension, slight or no renal insufficiency, minimal eyeground changes and a mild and protracted course, there still remains a group of cases that are difficult to place in any particular category. But in order to demonstrate fully the absence of any relation between the degree of epithelial infiltration and the height of the blood pressure, I have arbitrarily grouped the cases in two classes: the mild and the severe. Many cases are difficult to classify, but those with the highest manometric readings and the greatest degree of cardiac hypertrophy are placed in the latter group. Eighteen cases were marked by diastolic blood pressures of 130 mm. of mercury or over.

TABLE 11.—*Distribution of Cases of Hypertension in Which More Than One Section Through Both Lobes Was Examined*

Degree of Infiltration	Cases	Percentage of Total
1	5	9.2
2	14	25.9
3	17	31.4
4	11	20.5
5	7	12.9

TABLE 12.—*Distribution of Cases of Hypertension According to the Degree of Basophilic Invasion of the Posterior Lobe*

Degree of Infiltration	Mild Cases	Severe Cases
5	4	4
4	9	4
3	11	9
2	10	9
1	5	5

Table 12 shows the two groups of cases of hypertension distributed according to the degree of invasion of the posterior lobe. Of 31 cases of severe hypertension, 23 are distributed among the groups with lower degrees of basophilia, and of 39 cases of mild hypertension, 24 are distributed among the groups with slight degrees of infiltration. From moderate to marked infiltration is present in 13 of the latter cases while only 8 of the cases of severe hypertension reveal similar degrees of invasion. Thus, one must conclude that in this small series there is no definite relation between the degree of epithelial invasion and the height of the blood pressure. This deduction will appear obvious after the findings in the control series are reviewed. Details of the cases in the groups with basophilia of degrees 4 and 5 can be found in tables 19 and 20.

THE POSTERIOR LOBE IN THE CONTROLS

The total control series consisted of 60 males and 48 females. All had either normal or subnormal blood pressure readings during their period of observation in this institution or on previous hospitalizations elsewhere. The majority of the controls were patients with pulmonary tuberculosis, rheumatic or arteriosclerotic heart disease, neoplastic diseases of various types, blood dyscrasias, endocrine disturbances and various neurologic disorders. A few of the controls had died of acute medical and surgical conditions. The control group is shown distributed as to age and sex in table 13.

TABLE 13.—*Grouping of Controls with Respect to Age and Sex*

Age, Years	Males	Females
9 to 35	13	14
36 to 50	10	12
51 to 65	26	16
66 to 87	11	6

TABLE 14.—*Grouping of the Controls According to the Degree of Basophilic Invasion of the Posterior Lobe of the Hypophysis*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
1	6	13	17.5	10.0	27.0
2	18	20	35.1	30.0	41.6
3	15	10	23.1	25.0	20.8
4	14	4	16.6	23.3	8.3
5	6	0	5.5	10.0	0
6	1	1	1.8	1.6	2.0

The grouping of the 108 controls according to the degree of the basophilia of the posterior lobe is indicated in table 14.

If these findings are compared with those for the hypertensive group, one observes a slight preponderance (6.1 per cent) of hypertensive persons in the groups with higher degrees of basophilia. However, if one compares the relative age distributions, it is clear that there is a higher percentage of controls among the younger age groups. For example, 25 per cent of the controls were 35 years old or younger as against 1.4 per cent of the hypertensive persons, and 27.1 per cent of the hypertensive ones were 66 or older, while only 14.8 per cent of the controls fell in this age group. Therefore, if one compares the hypertensive and control groups, age for age, the difference in degree of basophilic invasion is insignificant. Table 15 shows the grouping of the controls who were over 35 years of age. However, since 81.4 per cent of the hypertensive

TABLE 15.—*Grouping of Controls Over 35 Years of Age According to the Degree of Basophilic Infiltration*

Degree of Infiltration	Males	Females	Percentage of		
			Total	Males	Females
1	4	7	13.5	8.5	20.5
2	12	14	32.0	25.5	41.1
3	14	8	27.1	29.7	23.5
4	11	4	18.5	23.4	11.7
5	5	0	6.1	10.6	0
6	1	1	2.4	2.0	2.9

TABLE 16.—*Comparison of the Hypertensive and Control Groups Over 50 Years of Age as to Degree of Basophilia of the Posterior Lobe*

Degree of Infiltration	Hypertensive Patients		Controls		
	Males	Females	Males	Females	Percentage of Total
1	3	7	4	5	15.2
2	3	8	10	8	30.5
3	12	5	10	4	23.7
4	8	3	8	4	20.3
5	5	2	4	0	6.9
6			1	1	3.3

TABLE 17.—*Grouping of Controls 50 Years of Age and Younger According to the Degree of Basophilic Invasion of the Posterior Lobe*

Degree of Infiltration	Males	Females
1	2	8
2	8	12
3	5	6
4	6	0
5	2	0

TABLE 18.—*Grouping of Persons Who Had Previously Been Subject to Hypertension*

Degree of Infiltration	Males	Females
1	2	0
2	1	0
3	2	0
4	4	1
5	0	1

TABLE 19.—*Data on Cases in Which the Neurohypophysis Showed Basophilic Infiltration of Degree 4*

Case	Age	Sex	Major Clinical and Anatomic Diagnoses	Period of Observation	Blood Pressure		Renal Function		Weight of Heart, Gm.
					Systolic	Diastolic	Specific Gravity of Urine	Blood Urea N	
1	38	M	Hodgkin's disease	15 mos.	88-100	56-60	1.018-27	8.1	180
2	58	M	Amytrophic lateral sclerosis; essential hypertension	5½ mos.	160	90-94	1.025	15.8	350
3	45	M	Bronchial carcinoma	8 mos.	110	60	1.010-12	6.0	470*
4	62	M	Chronic pulmonary tuberculosis; tuberculous pericarditis; pyopneumothorax	9 days	120	70	1.018	....	Slightly* enlarged; not weighed
5	58	F	Chronic pulmonary tuberculosis; diabetes mellitus	4½ mos.	80-100	40-70	1.006-20	8.8	190
6	42	M	Thrombo-angiitis obliterans; chronic pulmonary tuberculosis	10 yrs., 8 mos.	80-100	50-70	1.014-25	9-12	220
7	56	M	Antecedent hypertension; myocardial infarction; septicemia	17 days	130	90-100	1.020-23	26	400
8	55	M	Marked secondary anemia; hemangiomas of nose; hypertrophy and dilatation of heart due to anemia	3 yrs., 3 mos.	102-140	40-70	1.010-21	....	680
9	60	F	Chronic pulmonary tuberculosis; diabetes mellitus	1 yr., 7 mos.	118-20	50-80	1.007-20	9-17	250
10	58	F	Bronchial carcinoma; essential hypertension; hydropericardium	6 hrs.	194	94	.....	....	270
11	80	M	Carcinoma of stomach	17 days	126	66	1.016-18	18	300
12	35	M	Essential hypertension; encephalomalacia	4 mos., 2 wks.	170-190	110-130	1.015-19	23-72	550
13	35	M	Chronic pulmonary tuberculosis	3 mos., 2 wks.	106	72	1.017	....	320
14	56	M	Chronic lymphatic leukemia	2 mos.	100-114	64-70	1.014	23	350
15	64	M	Essential hypertension; encephalomalacia	2½ wks.	176	118	1.020	21	300
16	60	F	Antecedent hypertension; diabetes mellitus; myocardial infarction; encephalomalacia	1½ mos.	110	70	1.007-20	14-23	480
17	59	M	Carcinoma of bladder; essential hypertension	1½ mos.	160	90	1.008	16	360
18	31	M	Chronic pulmonary tuberculosis	5 mos.	94-98	38-70	1.010-17	9	280
19	54	M	Essential hypertension; melanosarcomatosis	5 days	140-155	108-116	1.016	....	410
20	66	M	Antecedent hypertension; bronchiectasis	3 mos.	134-155	66-90	1.014-15 (fixed)	33-43	560
21	54	F	Essential hypertension; diabetes mellitus; myocardial infarction; encephalomalacia	3½ wks.	160	90-100	.....	15	350
22	70	M	Essential hypertension; pulmonary emphysema; encephalomalacia	2 yrs., 3 mos.	180-204	84-119	1.007-25	....	400

TABLE 19.—*Data on Cases in Which the Neurohypophysis Showed Basophilic Infiltration of Degree 4—Continued*

Case	Age	Sex	Major Clinical and Anatomic Diagnoses	Period of Observation	Blood Pressure		Renal Function		Weight of Heart, Gm.
					Systolic	Diastolic	Specific Gravity of Urine	Blood Urea N	
23	67	M	Essential hypertension; diabetes mellitus; encephalomalacia	7 days	238	132	1.016	20	340
24	58	F	Essential hypertension; encephalomalacia; myocardial infarction	2 yrs., 10 mos.	170-230	95-130	1.022-25	11-14	500
25	50	F	Bronchial carcinoma	2 mos.	125	75	1.019	8-12	300
26	32	M	Rheumatic heart disease; subacute bacterial endocarditis; diffuse and embolic glomerulonephritis	2 mos.	140	80	1.010-12 (fixed)	39-49	370
27	74	M	Antecedent hypertension; cerebral hemorrhage	2 days	110	74	.....	....	600
28	60	F	Carcinoma of breast; diffuse carcinomatosis	2 wks.	154	88	1.024	23	270
29	66	M	Osteitis deformans; antecedent hypertension	3 yrs., 6 mos.	110	48	.....	....	620
30	68	M	Inanition of unknown origin; marked secondary anemia (hemorrhoids)	8 mos.	110-154	58-66	1.009-10	12	220
31	52	M	Rheumatic heart disease (aortic insufficiency); subacute bacterial endocarditis; chronic glomerulonephritis	3 mos.	160	40	1.011-17 (slightly fixed)	22	680
32	57	M	Chronic pulmonary tuberculosis	10 days	120	64	1.016-23	....	370
33	71	M	Essential hypertension; encephalomalacia	4 days	164	98	.....	43	350
34	61	M	Essential hypertension	4½ mos.	124-150	100-108	1.012-26	22-48	500
35	49	M	Essential hypertension; rheumatic heart disease (aortic insufficiency); subacute bacterial endocarditis of aortic valve	4 days	200	110-120	1.026	12.9-71.4	750
36	56	M	Tuberculosis of suprarenals; Addison's disease; myocardial infarction	6½ mos.	70-98	40-70	1.020-24	19-49	300

* Large person.

group were over 50 years of age as against 54.6 per cent of the controls, this comparison is still not entirely fair.

The percentage of males over 50 is higher than that of the females over 50 in both the hypertensive and the control group, but the ratio of males to females is higher among the controls. There are 1.5 males to 1 female in the hypertensive group and 1.68 males to 1 female in the control group. This discrepancy in sex ratio probably influences slightly the final distribution of cases.

Now, if one compares directly only groups over 50 years of age, the results are as indicated in table 16.

TABLE 20.—*Data on Cases in Which the Neurohypophysis Showed Basophilic Infiltration of Degree 5 and on Those in Which Degree 6 Was Found*

Case	Age	Sex	Major Clinical and Anatomic Diagnoses	Period of Observation	Blood Pressure		Renal Function		Weight of Heart, Gm.
					Systolic	Diastolic	Specific Gravity of Urine	Blood Urea N	
			Basophilic Infiltration of Degree 5						
1	55	M	Chronic pulmonary tuberculosis; tuberculous meningitis	8 days	110-140	60-80	1.018	....	Normal size
2	52	M	Essential hypertension	6 wks.	150-180	90-120	1.017-22	29	850
3	47	M	Chronic pulmonary tuberculosis	9 mos.	115	80	1.011-20	13	250
4	64	F	Carcinoma of gallbladder; diabetes mellitus; essential hypertension; encephalomalacia	2 days	170	120	1.017-23	49	650
5	62	M	Bronchial carcinoma	19 days	120-140	80-85	1.021	13-22	260
6	70	F	Essential hypertension; encephalomalacia	6½ mos.	180-210	80-102	1.024-26	18	650
7	51	M	Osteitis deformans; septicemia; myelopathy	5 mos.	120-150	56-70	1.014-20	15	350
8	73	M	Essential hypertension; myocardial infarction; uremia	3½ mos.	134-180 (220/118 during attacks of paroxysmal nocturnal dyspnea)	88-95	1.015-17 (fixed)	17-95	490
9	65	F	Essential hypertension; diabetes mellitus; myocardial infarction; encephalomalacia	1 mo.	220	160	.....	26-43	475
10	72	F	Antecedent hypertension; diabetes mellitus; myocardial infarction	4 mos.	120	68	1.012-14	11	450
11	59	M	Hypernephroma of suprarenal	2½ wks.	140	80	1.025	18	280
12	30	M	Primary sarcoma of brain	6½ mos.	90-100	50-70	1.020-32	7	300
13	61	M	Essential hypertension; myocardial infarction; diabetes mellitus; encephalomalacia	4 mos., 1 wk.	140-175	100-112	1.010-22	17-45	600
14	68	M	Essential hypertension; diabetes mellitus; myocardial infarction	2 mos.	130-160	84-110	1.020-30	15.4	460
15	56	M	Diabetes mellitus; essential hypertension; mitral stenosis and insufficiency; coronary occlusion	11 mos.	165-214	95-124	1.010-25	20-58	700
			Basophilic Infiltration of Degree 6						
1	80	F	Endothelioma of spinal dura; atherosclerosis of mitral valve and aortic valve; mixed cell adenoma of anterior lobe of pituitary	5 wks.	128-150	78-80	1.010-20	20	400
2	75	M	Cerebral hemorrhage; hypertrophy of prostate	2 mos., 1 wk.	120	65	1.006-13	37	300

Finally, the tendency for younger males to fall into the groups with the higher degrees of infiltration while the females of approximately the same age groups show lesser degrees of invasion is shown in table 17. The table shows that 34.6 per cent of the younger males presented significant degrees of basophilic infiltration while no female showed more than slight invasion. Tables 19 and 20 give details concerning the controls with basophilic infiltration of degrees 4, 5 and 6.

THE POSTERIOR LOBE IN CASES IN WHICH THERE WERE EVIDENCES OF ANTECEDENT HYPERTENSION

There are available for study 11 cases in which there were clinical and anatomic evidences of a preexisting essential hypertension. All the patients had cardiac hypertrophy, which was considerable in 6. In none was there any evidence of valvular disease or glomerulonephritis. Normal blood pressure readings were obtained in all. Seven showed healed infarcts of the myocardium. Only 2 were females. The ages were as follows: 52, 54, 56, 60, 65 (2), 70, 72 and 74. The grouping according to the degree of basophilia of the posterior lobe is shown in table 18. It may be seen that slightly more than half showed moderate to marked invasion. However, the series is too small to allow one to draw conclusions.

It is difficult to classify this series. One of the patients, a man 52 years old, whose blood pressure was 120 systolic and 80 diastolic, showed readings of 200 systolic and 140 diastolic during attacks of paroxysmal pulmonary edema. This elevation of tension occurred in the presence of severe myocardial damage. The posterior lobe was free from invading elements. In spite of extensive infarction, the myocardium was able to maintain a considerable elevation of intravascular tension for short periods. If one assumes that marked basophilia of the posterior lobe is an indicator of an excessive production of a pressor substance, it becomes difficult to understand why persons with significant epithelial infiltration show normal blood pressure readings. The presence of myocardial damage is of itself not sufficient cause for a marked reduction of intravascular tension, for old myocardial infarcts of moderate to marked extent were present in not less than 13 of the 70 persons who had high blood pressure readings. The mechanism of the reduction of blood pressure in these cases is not clear, but it is not unlikely that a peripheral mechanism comes into play.

COMMENT

The evidence indicates that the invasion of the pars nervosa by basophilic cells bears no relation to increased vascular tension. This interesting histologic phenomenon has been observed and commented on by many investigators since 1901, but Cushing was the first to

attribute to it a rôle of special importance in the physiology of the neurohypophysis. It is easy to understand why not a single worker in the field of endocrinology has specifically related these invading epithelial elements to disturbances of vascular tension. Investigators with the extensive experience of Erdheim, Kraus, Aschoff, Berblinger, Lucien, Guizzetti and their pupils had encountered this phenomenon in so large a variety of diseases that they could not correlate their histologic observations with any particular physiologic dysfunction. It is incorrect to state that workers in this field during the past twenty years were not cognizant of a possible physiologic rôle of these invading cells. The total lack of any constant relation between basophilic infiltration of the nerve tissue and a particular physiologic disorder or group of disorders made perilous any generalizations regarding the function of these cells. There remained only the changes due to aging, which have been commented on by many authors. My own observations, based on 189 glands, are in accordance with the conclusions of the European workers.

The instances gathered from the literature and my own observations demonstrate that essential hypertension in all its phases is not characterized by an inordinate degree of basophilic infiltration of the pars nervosa. If, as Cushing stated, this cellular infiltration is an index of neurohypophyseal hyperactivation, one can add that in essential hypertension there is no excessive secretion of hormone of the posterior lobe as part of the physiologic disturbance. However, there is no direct proof that the basophilic granules, or Herring's hyaline globules, represent a pressor hormone (Maurer and Lewis [45]). One cannot estimate the activity of the pars intermedia by morphologic methods.

Recent studies by Byrom and Wilson [46] and Hoyle [47] seem to indicate that some of the older observations on the presence of pituitary-like substances in the blood and spinal fluid of women with eclampsia and essential hypertension, respectively, may have been erroneous. Page [48] showed the fallacy of building hypotheses on the etiology of hypertensive disorders by the demonstration of pressor substances in human blood serum. Capps and his collaborators [49] demonstrated a pressor substance in the urine, but not in the blood, of normal and of hypertensive subjects. Collip [50] demonstrated a pressor substance in a large variety of tissues.

45. Maurer, S., and Lewis, D.: J. Exper. Med. **36**:141, 1922.

46. Byrom, F. B., and Wilson, C.: Quart. J. Med. **27**:361, 1934.

47. Hoyle, C.: Quart. J. Med. **26**:549, 1933.

48. Page, I.: J. Clin. Investigation **12**:703, 1934.

49. Capps, R. B.; Ferris, E. B.; Taylor, F. H. L., and Weiss, S.: J. Clin. Investigation **12**: 722, 1934.

50. Collip, J. B.: J. Physiol. **66**:416, 1928.

On the other hand, these inwandering basophils must have some physiologic significance. Their exact mode of origin is in dispute. Aschoff,[51] Erdheim,[52] Berblinger,[27] Kasche,[53] Dayton,[54] Rasmussen,[30] Guizzetti [55] and Plaut [56] have discussed this problem fully. It is impossible to reconcile the two main points of view: namely, an origin from the pars intermedia, and an emigration from the anterior lobe. One may definitely deny the existence of a human pars intermedia comparable to that in lower animals, but one must admit that between the glandular tissue and the nerve tissue in the hypophysis there remain rudimentary structures which represent the pars intermedia of the human species. Further, the vestigial nature of this tissue does not signify an absence of functional activity. In all probability, the hormone of the posterior lobe is elaborated by these vesicles which lie adjacent to the nerve tissue.

I have indicated that the occurrence and extent of the invasion of the posterior lobe are related in some way to the aging of the organism and possibly to some sex factor as well. The tendency for a number of males in the prime of life to exhibit this phenomenon cannot be totally explained as accidental. The data presented by Kiyono, Höppli and Orlandi are equally suggestive, and recently Rasmussen [57] stated that the parenchyma of the pars intermedia is slightly but significantly larger in males. However, a much larger series of cases will have to be studied before any valid conclusions can be drawn regarding the influence of other endocrine glands.

In regard to the immediate stimulating factors in basophilic invasion one must admit that while prolonged nervous stimulation from hypothalamic centers may play a rôle in the proliferation and infiltration of the basophilic cells, it is difficult to conceive of an acute epithelial invasion of the posterior lobe due to a series of nervous discharges from these centers. A mechanical theory, such as Bucy proposed, cannot explain the presence of basophils in the posterior lobe in cases in which large colloid-filled cysts widely separate the two lobes. One is tempted to accept a humoral stimulating mechanism for the proliferation of the epithelial cells of Rathke's cysts. The hormonal factors which may be involved in this mechanism are as yet unknown. But certainly the safest view at present is that the basophilic invasion of the neurohypophysis is the result of some form of stimulation.

---

51. Aschoff, L.: Beitr. z. path. Anat. u. z. allg. Path. **84**:273, 1930.
52. Erdheim, J.: Ergeb. d. allg. Path. u. path. Anat. **21**:482, 1926.
53. Kasche, F.: Ztschr. f. mikr.-anat. Forsch. **6**:13, 1926.
54. Dayton, T. R.: Ztschr. f. Anat. u. Entwcklngsgesch. **81**:359, 1926.
55. Guizzetti, P.: Sperimentale, Arch. di biol. **80**:665, 1927.
56. Plaut, A.: Anat. Anz. **68**:408, 1930.
57. Rasmussen, A. T.: Am. J. Anat. **55**:253, 1934.

SUMMARY AND CONCLUSIONS

The pituitary glands from 70 persons with essential hypertension, 11 persons with evidence of antecedent hypertension and 108 with various nonhypertensive diseases were studied histologically.

Those from persons with essential hypertension showed no greater degree of basophilic invasion of the pars nervosa than those from nonhypertensive ones when groups of approximately the same ages were compared.

The invasion of the posterior lobe by basophils is in some way related to the aging of the organism and possibly to some sex factor as well. The immediate stimulating factors are unknown.

There is no morphologic evidence to support the hypothesis that essential hypertension and eclampsia gravidarum are due to a hyperactivation of the neurohypophysis by basophilic cells.

HIGH FREQUENCY ELECTRIC FIELDS AND ROENTGEN RAYS

EFFECTS ON COMPENSATORY HYPERTROPHY OF THE KIDNEY

RAYMOND B. ALLEN, M.D.*
NEW YORK
AND
CAROL B. PRATT, PH.D.
AND
CHARLES SHEARD, PH.D.
ROCHESTER, MINN.

A type of high frequency or short wave electric oscillator, designed and built in the research laboratories of the General Electric Company and made available for investigations on the effects of this form of energy on biologic processes, was used in the present experiments. Essentially, it is a short-wave radio generator in which the output is fed to large condenser plates rather than to an antenna. The apparatus operates over a range of frequency of from 15,000 to 40,000 kilocycles (wavelengths of from 7.5 to 20 meters) with an approximate output of power of from 150 to 400 watts.

One effect of the high frequency electric field on warm-blooded animals which is now well established is an elevation of the temperature of the body; this is undoubtedly accompanied by an increase in the flow of blood.

An investigation was planned to determine whether the high frequency field would stimulate renal hypertrophy after unilateral nephrectomy.

EXPERIMENTAL DATA

As a preliminary to this work two rabbits were treated with the high frequency field, and the renal temperatures were obtained by means of a thermocouple, contained in a suitable needle, which was on open-circuit while the electric field was in operation. While the animal was under anesthesia the needle was thrust into the substance of the kidney. The readings demonstrated that the renal temperatures were practically identical with the rectal readings. The rectal temperatures of these two animals were elevated approximately 0.7 C. (1.26 F.) following exposure of the animals to the high frequency field.

---

* Fellow in Urology, the Mayo Foundation.

From the Division of Physics and Biophysical Research, the Mayo Clinic.

The work reported in this study was done at the Institute of Experimental Medicine, the Mayo Clinic.

Seven rabbits, from two litters comprised of animals of the same age and breed, were used; three of these rabbits were treated with the high frequency field, and four were kept as controls. All seven rabbits were operated on the same day, the right kidney being removed under ether anesthesia. Three times a week thereafter for the duration of the experiment (twelve weeks) each of the three experimental animals was exposed to the high frequency field for five minutes through the region of the remaining kidney. The condenser plates, which measured 2.5 by 3 inches (6.5 by 7.5 cm.), were 5 inches (12.5 cm.) apart, and the abdomen of the rabbit was interposed between them. A current of from 0.033 to 0.065 ampere per square inch was employed, at a frequency of 27,500,000 cycles (wavelength, 11 meters). During the treatment the rabbit was maintained in the prone position in a special neck and girdle stock which was built so that the animal was immobilized; thus burns from contact with the condenser plates were prevented.

A comparison of the data on the control and those on the experimental animals reveals that practically the same degree of renal

Comparison of the Weights of Livers and Spleens with the Weights of Bodies of Animals Treated with the High Frequency Electric Field

Series	Animal	Sex	Weight, Gm.			Relation of Weights, Index Number	
			Body	Liver	Spleen	Liver to Body	Spleen to Body
Control	1	M	2,170	69.6	1.24	32.07	0.57
	2	F	1,661	43.0	0.96	25.88	0.58
	3	M	1.518	50.2	0.95	33.07	0.62
	4	F	1.957	56.4	0.88	28.82	0.45
	Mean		1,826	54.8	1.01	29.96	0.56
Experimental	5	M	1,952	67.2	1.50	34.42	0.77
	6	M	1,800	61.7	1.50	34.28	0.83
	7	F	2,140	69.2	1.30	32.34	0.61
	Mean		1,964	66.0	1.43	37.01	0.74

hypertrophy occurred in each series. Apparently the high frequency electric field, under the conditions of this experiment, failed to exert either a stimulating or an inhibiting influence on the hypertrophic process. It appears, however, that the livers and spleens of the three experimental animals were significantly larger than those of the control animals (table). A part of the liver and all of the spleen were undoubtedly included in the action of the high frequency field during the treatments. The amounts of hepatic and splenic tissue, as indicated by the index numbers (amount of tissue per unit of body weight), are also apparently significantly greater.

The liver plays an important, but at present little understood, rôle in the heat-regulating mechanism of the body. The spleen is known to change in size according to demands on the blood flow, and it is influenced by certain infectious states. The fact that the livers and spleens of rabbits apparently were affected by the high frequency field is of interest and is being investigated further.

Small doses of roentgen rays have been considered by some investigators to exert a stimulating effect on growth; in experiments with young plants the evidence is most convincing.

Two litters of rabbits were employed in studying the effect of roentgen rays on compensatory renal hypertrophy. The first litter comprised three controls and one experimental animal, the animals being treated over a period of nine weeks; and the second litter comprised two controls and two experimental animals, these animals being treated over a period of eight weeks.

The dose of roentgen rays for this experiment was fixed at 59 roentgens, which was obtained with 120 kilovolts and 5 milliamperes of current over a period of one minute, with a 2 mm. aluminum filter. This exposure was repeated three times weekly. Care was taken to screen out other organs. This was easy to accomplish because the kidney could be palpated in its entirety through the abdominal wall.

The same relative degree of renal hypertrophy occurred in the experimental and in the control animals.

SUMMARY

Compensatory renal hypertrophy in rabbits, under the conditions of these experiments, was not influenced by treatment with the high frequency electric field or by the doses of roentgen rays used in these experiments.

The livers and spleens of the rabbits which were treated with a high frequency field were larger than those of control animals.

INFECTION WITH TRYPANOSOMA EQUIPERDUM

DAVID PERLA, M.D.
NEW YORK

The course of infection with Trypanosoma equiperdum and the pathologic changes associated with it were studied in a large series of normal adult albino rats. The observations presented in the following communication were made a basis of comparison in subsequent studies of certain factors influencing the natural resistance of the animal to this disease.

THE LITERATURE

T. equiperdum in the rat and mouse produces an acute disease. Taliaferro and Taliaferro[1] observed that the parasites are confined to the blood stream and multiply there continuously, causing death of the host within from three to six days after injection. They include the disease in the group of trypanosomal infections of the continuous type, that is, a type to which no resistance is manifest.

The chemical changes in the course of the infection and the lethal factors in the disease in rats have been adequately investigated. According to Andrews, Johnson and Dormal,[2] rats die of asphyxia due to obstruction of the circulation in the pulmonary capillaries by agglutinated trypanosomes. Pulmonary edema results. This leads to anoxemia and a nonvolatile, uncompensated acidosis. Anoxemia favors central necrosis of the liver, interfering with its glycogenic and glycogenolytic functions and ultimately producing hypoglycemia. A moderate anemia is noted. Linton[3] made observations as follows: The carbon dioxide-combining power of the serum is markedly lowered early in the infection, the nonprotein nitrogen and uric acid rise in the terminal stages, the cholesterol remains unchanged throughout, but the lecithin is increased by from 20 to 50 per cent. The hepatic glycogen is decreased in the early stages and is completely depleted late in the infection. The blood sugar remains normal till very late in the disease, but drops markedly during the last twenty-four hours. The oxygen-carrying capacity of the blood is diminished.[3] Recently Raffel[4] reported a relapsing type of infection in rats receiving injections of small numbers of organisms, and he studied the presence of the so-called "Rieckenberg antibody" in the serum. Raffel's article includes a review of the literature on the phenomena of immunity in the trypanosomal infections. He observed a higher degree of natural resistance in female rats than in male rats.

METHOD OF STUDY

The strain of T. equiperdum was obtained from Dr. Reimer of the Burroughs Wellcome Laboratories. It was transferred in rats every third day by intraperi-

---

From the Laboratory Division, Montefiore Hospital.

1. Taliaferro, W., and Taliaferro, L. G.: Am. J. Hyg. **2**:264, 1922.
2. Andrews, J.; Johnson, C. M., and Dormal, V. J.: Am. J. Hyg. **12**:381, 1930.
3. Linton, R. W.: J. Exper. Med. **52**:695, 1930.
4. Raffel, S.: Am. J. Hyg. **19**:446, 1934.

toneal injection. The rats used were originally of Wistar stock and were raised in the laboratory of the Montefiore Hospital during the past twelve years. These were carriers of Bartonella muris. In addition, the infection was studied in ten Wistar rats free from latent infection with B. muris. No essential differences were observed in the trypanosomiasis in these two groups of rats. The factors of age and diet were kept constant.

At the time of the injection of the trypanosomes into the animals, the number of trypanosomes per cubic centimeter was readily estimated and the desired infecting dose obtained by dilutions of the blood in physiologic solution of sodium chloride. All injections were made intraperitoneally. The rats were from 3 to 4 months of age.

Three groups of rats were used. One group of twenty adult rats received 2,000,000 trypanosomes each; a second group of sixteen rats received 100,000 trypanosomes each; a third group of eight rats received 10,000 trypanosomes and a fourth group of ten rats 2,000 trypanosomes each. Red cell counts were made every second day, and smears of the peripheral blood were examined daily. With the larger doses, smears were made at twelve hour intervals.

COURSE OF THE INFECTION IN THE NORMAL ALBINO RAT

When overwhelming numbers (2,000,000) of trypanosomes were injected, the infection was fatal within from seventy-two to ninety-six hours. Within twenty-four hours, in some instances, the trypanosomes appeared in the blood. They rapidly increased in number, and at the end of forty-eight hours there were often more than 500,000 trypanosomes per cubic millimeter. On the third day, the count was frequently more than 2,000,000. Developmental forms were observed in the peripheral blood during the entire period of the infection though most of the parasites appeared mature. During the last day of the infection, many more younger forms were present, and dividing large forms were infrequent. The rats appeared well until a few hours before death; then they remained quiet and grew feeble, their hair became ruffled, and they died with signs of convulsions and severe toxemia. The trypanosomes underwent rapid disintegration after the death of the animal.

The infection with T. equiperdum showed the usual course of fatal trypanosomal infections as seen in rats and mice. The parasites appeared in the blood after a short period of incubation and increased in numbers steadily until the death of the host.

Taliaferro [5] noted that the coefficient of variation of infection with Trypanosoma rhodesiense in the mouse remained fairly high throughout the infection with no indication of a progressive change, and the number curve showed a steady, rapid rise to death after a period of incubation of four days. The coefficient of variation of infection with T. equiperdum is essentially similar to that in other types of fatal trypanosomal infections of rats and mice. The coefficient of variation

5. Taliaferro, W.: The Immunology of Parasitic Infections, New York, Century Company, 1930.

was estimated by Taliaferro and Taliaferro.[1] For the first day after trypanosomes appeared in the blood it was 7.34 per cent. It rose on subsequent days until at the death of the rat on the sixth day it was 10.94 per cent.

In the rats infected with T. equiperdum as in mice infected with T. rhodesiense, reproduction occurred at an approximately constant rate. Further, the organisms increased in the blood according to a geometric progression. This was not, of course, mathematically true with T. equiperdum, since the trypanosomes may die off as a result of unfavorable cultural conditions in the host late in the disease. From the constant rates of reproduction and accumulation in the blood, however, it is apparent that no resistance was acquired by the host which either affected the rate of reproduction of the parasites or destroyed them after they developed; that is, there was no evidence of reproduction-inhibitive antibodies (Taliaferro) or of trypanolysins such as are found in animals infected with Trypanosoma lewisi.

Relation of Duration of Infection to Number of Injected Parasites.—With smaller infecting doses, the duration of life of the rats after injection was somewhat prolonged. In part, this was due to a prolongation of the interval between the injection of the parasites and their appearance in the blood. With doses of 2,000 trypanosomes, this interval was from three to six days. Following the appearance of the parasites in the blood, the curve of the number of trypanosomes per day was approximately the same as with overwhelming doses. In some instances, however, the rats lived for from sixteen to nineteen days after the injection of the parasites, or for from ten to fourteen days after the trypanosomes first appeared in the blood stream.

With injection of 2,000 trypanosomes, almost half of the rats showed no evidence of infection. It has been the experience in this laboratory that if trypanosomes are found in the peripheral blood, the infection will end fatally. In instances of abortive infection, no trypanosomes were found in the blood smears. The relapsing type of infection recently described by Raffel[4] was not observed in this stock.

In the rats subjected to injection of 20,000,000 trypanosomes each the average duration of life was three and six-tenths days. In the group receiving 2,000 trypanosomes each the average duration of life in those with fatal infections was fourteen and a half days.

RELATIVE LYMPHOCYTOSIS IN INFECTION WITH T. EQUIPERDUM

There was usually little or no leukocytosis. However, some rats showed a rise in the total number of white cells to 25,000 per cubic millimeter in the last twenty-four hours of the infection. Occasionally during the first day of the infection a slight rise occurred, with a fall

to a normal level in the next few days. The lymphocytes were increased in number. The relative lymphocytosis reached its peak late in the disease, and many lymphoblasts appeared in the peripheral blood. The increase in lymphoid cells was associated with a marked stimulation of the lymphoblastic tissue of the spleen and lymph nodes.

NATURE OF THE SECONDARY ANEMIA IN INFECTION WITH T. EQUIPERDUM

It was noted that in many instances rats infected with T. equiperdum and surviving more than five days acquired a moderate secondary anemia. The red cell count dropped from 10,000,000 to below 5,000,000 per cubic millimeter and the hemoglobin to below 40 per cent (Dare). The color index was low. The anemia developed on the fifth or sixth day, though it occasionally began on the fourth day, after the injection of trypanosomes. It became progressively severe if the rat survived, and in one instance the hemoglobin was 38 per cent on the ninth day. The anemia was unassociated with signs in the peripheral blood of erythrocytic regeneration. No normoblasts were observed, although an occasional Jolly body was seen. Moderate poikilocytosis, anisocytosis and polychromatia were noted. The number of reticulocytes was not increased. In general, the severity of the anemia bore a relationship to the number of trypanosomes, although occasionally the anemia began early in the disease.

Since the rats used in these experiments were carriers of B. muris it was thought that severe injury of the spleen by T. equiperdum may have resulted in a flare-up of the latent bartonella infection with anemia. This occurs in rats infected with T. lewisi, which induces a disease that severely injures the spleen and lasts from thirty to forty days.[6] Examination of many smears of blood from rats infected with T. equiperdum in which a secondary anemia occurred failed to reveal the presence of B. muris. Apparently the animals did not survive long enough after severe functional injury to the spleen and the macrophage system to acquire the anemia[7] associated with B. muris.

To eliminate the possible influence of latent infection, the course of the infection with T. equiperdum was studied in ten Wistar rats that were free from latent infection with B. muris. Each of these was given an injection of 2,000 trypanosomes obtained from an infected guinea-pig. Of these, four acquired a moderate secondary anemia from the fifth to the seventh day. The secondary anemia of rats

6. Marmorston-Gottesman, J.; Perla, D., and Vorzimer, J.: J. Exper. Med. **52**:587, 1930.

7. In general, the anemia associated with the presence of B. muris develops in from five to ten days after splenectomy.

infected with T. equiperdum is apparently, therefore, independent of B. muris.

An attempt was made to detect the presence of a hemolytic substance in the blood of rats heavily infected with T. equiperdum.

Two rats were each infected with 2,000 trypanosomes. Nine days later the trypanosome count was 1,568,000 and 2,200,000 per cubic millimeter of blood. A moderate secondary anemia had developed (about 5,000,000 red blood cells per cubic millimeter with a hemoglobin content of 75 per cent). Two cubic centimeters of blood was removed from each rat, and the samples were pooled and diluted with equal parts of isotonic sodium citrate and physiologic solution of sodium chloride. The diluted blood was immediately passed through a Zeiss filter. (A sample of this was cultured and found to be sterile.) The clear fluid was injected into three young rats, 4 weeks of age, in amounts varying from 0.5 to 1.5 cc. The blood of two normal adult rats was similarly treated and injected into three young rats in the same amounts.

As will be noted in the protocol (table 1), the cell-free filtrate of the diluted blood of rats infected with trypanosomes induced a moderate anemia in three young rats. No effect was noted from the filtered blood obtained from normal animals and similarly injected into young rats. The blood of the young rats in which an anemia was induced within from twenty-four to forty-eight hours when injected into other young rats produced no anemia. It was apparent, therefore, that the hemolytic toxic agent was not transmissible beyond a single passage, and it is unlikely that the agent was infectious.[8]

It seems, then, that some substance is elaborated by the trypanosomes which severely injures and destroys circulating red cells. This toxic substance is hemolytic when injected into young rats.

The anemia associated with an infection by T. equiperdum is not due to a flare-up of a latent infection with B. muris such as is observed in rats infected with T. lewisi.

IRON AND COPPER CONTENT OF THE LIVER AND SPLEEN IN INFECTION WITH T. EQUIPERDUM

From the study of the pathologic aspects of the disease it was evident that phagocytic activity of the cells of the macrophage system occurs, with the ingestion of red blood cells. This is observed in the endothelial and reticular cells of the spleen and to a lesser extent in the Kupffer cells of the liver, and suggests a hemolytic anemia. The macrophage cells are active in the ingestion of trypanosomes, and it is likely that this greatly enhances their capacity for erythrophagocytosis.

8. In previous studies of the anemia caused by infection with B. muris it was observed that the infection cannot be transmitted to young rats by cell-free filtrates of the blood of splenectomized rats heavily infected with B. muris (Marmorston-Gottesman, J., and Perla, D.: J. Exper. Med. **52**:121, 1930).

It would be expected, therefore, that in this type of secondary infectious anemia the storage of iron in the liver and spleen would greatly increase. Little or no iron pigment, however, was noted in the Kupffer cells, but some was observed in the endothelial and reticular cells of the spleen. Chemical analyses were made for the iron and copper content of the liver and spleen of rats infected with T. equiperdum. The analyses were begun soon after the death of the animals.[9]

It will be noted from table 2 that the concentration of iron in the liver of infected rats was from two to three times as great as in that of uninfected rats of the same age group. In rat 31, the duration of life after infection with trypanosomes was nineteen days, and the concentration of iron in the liver was five times the normal value.

TABLE 1.—*Toxic Hemolytic Effect in 3 Week Old Rats of Injections of Cell-Free Filtrate of Diluted Blood from Rats* Infected with T. Equiperdum*

Rat	Amount Injected, Cc.		Blood Count						
			Before Injection	Days After Injection					
				1	2	3	4	5	6
10.....	0.5	R.B.C.†	6,600,000	6,200,000	6,000,000	4,500,000	3,800,000	5,000,000	7,000,000
		Hgb.	90%	85%	70%	63%	60%	80%	92%
11.....	1.0	R.B.C.	7,200,000	7,500,000	5,700,000	4,300,000	4,000,000	6,000,000	7,000,000
		Hgb.	90%	90%	70%	65%	50%	80%	95%
12.....	1.5	R.B.C.	6,400,000	4,800,000	4,500,000	6,500,000	7,000,000		
		Hgb.	90%	65%	60%	98%	100%		
13 (control)...	0.5	R.B.C.	6,200,000	6,400,000	6,700,000	6,100,000	6,900,000		
		Hgb.	95%	95%	98%	100%	100%		
14 (control)...	1.0	R.B.C.	5,900,000	6,100,000	5,900,000	6,400,000	6,100,000		
		Hgb.	98%	100%	102%	98%	98%		
15 (control)...	1.5	R.B.C.	6,000,000	5,900,000	6,100,000	6,200,000	5,800,000		
		Hgb.	102%	98%	99%	102%	100%		

* At the time of injection the red blood cell counts of the donor rats were 5,600,000 and 4,200,000 and the hemoglobin contents 55 and 38 per cent.

† Three week old rats normally have blood counts between 5,500,000 and 7,000,000 per cubic millimeter.

The concentration of iron in the spleen as determined by chemical methods was definitely decreased, although histologically iron pigment was readily observed on section. The concentration of copper in the liver was unchanged, but there was a marked decrease in the copper content of the spleen. It is difficult to explain the discrepancies between the histologic observations and the chemical results. It is suggested that the exhaustion of the reticular and endothelial cells of the spleen at the end of the infection results in a release of both iron and copper stored in these cells, with an increased concentration of iron in the liver. Further, it seems that the iron in the liver is stored as a ferrous salt, not a ferric salt, and therefore fails to give the histologic microchemical test for iron pigment. This may be due to an exhaustion of oxidative ferments in the hepatic cells preventing the conversion of ferrous to ferric salts.

9. Dr. Marta Sandberg made the chemical analyses.

It is probable that the disturbance in the metabolism of iron and copper in rats infected with T. equiperdum is in part a result of severe injury to the spleen. In studies reported in another communication, Sandberg and Perla [10] observed the effect of splenectomy in bartonella-free rats on the metabolism of copper and iron. It was found that the excretion of copper exceeded the intake, and that a negative copper balance was established from two to four weeks after splenectomy, which persisted. The retention of iron, however, increased. Apparently severe injury to the spleen by a protozoan infection may have a similar effect. It is possible that the disturbance in the metabolism of copper contributes to the production of the secondary anemia in rats infected with T. equiperdum.

TABLE 2.—*Iron and Copper Content of the Liver and Spleen of Albino Rats Infected with T. Equiperdum**

		Liver		Spleen	
Rat	Duration of Infection, Days	Copper, Mg. per 100 Gm. Dried Weight	Iron, Mg. per 100 Gm. Dried Weight	Copper, Mg. per 100 Gm. Dried Weight	Iron, Mg. per 100 Gm. Dried Weight
30	16	....	46.69	....	.....
31	19	....	122.50	....	.....
32	6	1.41	60.39	....	98.97
33	6	3.58	71.85	....	72.16
34	6	2.25	78.66	2.93	87.61
35	6	1.86	53.42	2.41	116.40
36	6	1.85	48.74	3.01	84.14
37	Control	3.25	23.22	....	.....
38	Control	2.87	28.15	....	.....
39	Control	2.20	22.77	....	.....
40	Control	2.34	25.48	....	.....
41	Control	1.49	33.55	....	.....
42	Control	1.47	35.36	....	105.70
43	Control	1.66	29.88	....	160.30
44	Control	....	.....	6.64	128.30
45	Control	....	.....	7.99	153.20
46	Control	....	.....	7.30	134.70
47	Control	....	.....	6.49	.....
48	Control	....	.....	7.17	.....
49	Control	....	.....	6.01	.....
50	Control	....	.....	....	.....

* All rats in this series are of Bartonella carrier stock.

INFLAMMATORY RESPONSE TO T. EQUIPERDUM INJECTED INTRAPERITONEALLY

The fate of the trypanosomes injected intraperitoneally and the cellular reaction to their presence were studied in a series of eighteen rats, each given 50,000,000 trypanosomes.

Method.—Three cubic centimeters of the blood of a rat severely infected with the trypanosomes was added to a solution containing 2 cc. of isotonic sodium citrate solution and 5 cc. of isotonic dextrose solution. The mixture was centrifugated at low speed for five minutes to remove the red blood cells, and then the gray-white layer of trypanosomes, with the supernatant diluted plasma, was pipetted off. This suspension was centrifugated at high speed for fifteen minutes,

10. Sandberg, M., and Perla, D.: J. Exper. Med. **60**:395, 1934.

the supernatant fluid discarded and fresh dextrose saline solution added. The washed trypanosome suspension was then injected in amounts of 0.5 cc. The number injected was estimated in the usual manner in smears of blood known to be normal by determining the ratio of trypanosomes to red cells.

One rat was killed every ten minutes after injection for the first hour and at the end of two and one half, four and twenty-four hours. Just prior to anesthetizing the rat, 2 cc. of dextrose citrate solution was injected intraperitoneally. The peritoneal cavity of the rat was immediately exposed, care being taken to avoid small vessels and bleeding into the cavity. The fluid was pipetted off from the lumbar gutters and centrifugated at high speed for twenty minutes. Smears were made of the sediment and stained with Wright's stain. Differential counts of the cells were made from these smears. The study was repeated on different days. On a third set of rats similarly infected with trypanosomes, cell counts of the undiluted peritoneal exudate were made.

Similar studies were made on rats given intraperitoneal injections of 0.5 cc. of plain broth.

TABLE 3.—*The Inflammatory Response to T. Equiperdum Injected Intraperitoneally*

	Rat	Interval After Injection	Differential Count of the Exudate					
			Mono	SL	PME	PMN	Mast	Tryp
Each rat received an injection of 50,000,000 trypanosomes suspended in 0.5 cc. of dextrose citrate solution	1	10 min.	42%	42%	14%	0	2%	4+
	2	20 min.	45%	1%	47%	0	8%	4+
	3	30 min.	28%	5%	57%	0	10%	3+
	4	40 min.	55%	9%	24%	7%	5%	2+
	5	50 min.	60%	2%	13%	13%	11%	1+
	6	60 min.	35%	10%	30%	8%	17%	
	7	2½ hrs.	24%	4%	0	64%	8%	+
Controls: Each rat received an injection of 0.5 cc. of broth	8	10 min.	4%	87%	1%	2%	6%	
	9	20 min.	69%	6%	10%	7%	8%	
	10	30 min.	60%	20%	3%	7%	10%	
	11	40 min.	72%	10%	2%	11%	5%	
	12	50 min.	70%	11%	4%	5%	10%	
	13	60 min.	65%	15%	1%	13%	6%	
	14	2½ hrs.	60%	14%	2%	16%	6%	

Mono = mononuclear phagocytes (clasmatocytes); SL = small lymphocytes; PME = eosinophilic polymorphonuclear leukocytes; PMN = neutrophilic polymorphonuclear leukocytes; Mast = mast cells; Tryp = trypanosomes—relative numbers expressed by 1 to 4 plus.

The results of one set of experiments are recorded in table 3. There was an immediate outpouring of mononuclear phagocytes (macrophages) and eosinophils within ten minutes. In the following twenty minutes the number of eosinophilic leukocytes increased to more than 50 per cent of the cellular exudate. During the same interval mast cells appeared in increasing numbers. The maximal mast cell response was observed after one hour (17 per cent). Neutrophilic leukocytes began to appear after forty minutes and increased rapidly after two and a half hours to 64 per cent. There was a corresponding drop in the eosinophils. The monocyte count continued high. The lymphocytic response was not significant after the first ten minutes. The cellular response to the injection of broth was different. Few eosinophils were observed, and the exudate was predominantly composed of macrophages and some mast cells.[11]

11. The macrophage response to injections of broth in the pleural cavity is well known (Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:388, 1923).

The trypanosomes rapidly decreased in number. At two and a half hours only a few were observed. In other experiments in which the rats were given injections of 1,000,000 trypanosomes or less, the trypanosomes were no longer to be seen within one hour. (In some instances they were still present twenty-four hours later.) During the period in which trypanosomes were present, they showed intense reproductive activity. They grew to a considerable size, to a degree not observed in the peripheral blood at the height of infection, and they divided rapidly. These large forms were observed within from ten to twenty minutes. Phagocytosis by large macrophages was distinctly manifest. Often the nuclear part of the body of a trypanosome as well as the blepharoplast was engulfed, and the flagella end was still outside the cell. Partly digested trypanosomes were seen within the phagocytic cells. The cytoplasm of the trypanosomes was not distinguishable from the cytoplasm of the phagocytes, but nuclei and blepharoplasts in various stages of disintegration were apparent. Eosinophilic leukocytes or neutrophilic leukocytes were never observed to participate in the phagocytic process. It was not possible to note phagocytosis of trypanosomes by mast cells owing to the deep-staining granules, but apparently these cells were phagocytic. The trypanosomes adhered to and surrounded the macrophages and often the eosinophils. Agglutination of trypanosomes even in centrifugated sediments was rarely observed. In another series of rats peritoneal exudates were examined by the hanging drop method at the same intervals and studied microscopically for evidence of phagocytosis in vitro. The trypanosomes remained active for twenty-four hours and showed no tendency toward clumping; occasionally actual division could be observed. The activity of a dividing trypanosome slowed down considerably during the process and in the hanging drop preparations continued during a period of from fifteen to thirty minutes. Phagocytosis was only rarely observed, owing to the difficulty of maintaining active ameboid motion of the mononuclear cells for any considerable period of time. Not infrequently the trypanosomes stuck to the surface of the mononuclear phagocyte or to the surface of the mast cell, and it was apparent that great effort was expended in swimming out of the sphere of attraction. The trypanosomes of this strain do not swim such great distances or so rapidly as T. lewisi observed in similar preparations, and the individual activity of single parasites can be intimately observed for long periods. The movements of the flagella and undulating membrane are clearly manifest. The trypanosome moves forward in the same direction as its flagella. It revolves and draws its protoplasm forward, and the varying positions of the nuclear body are clearly seen.

It is apparent, therefore, that though many of the trypanosomes are destroyed within the peritoneal cavity by the phagocytic macrophages,

those that escape phagocytosis continue to divide rapidly. They probably enter the blood stream within a few minutes. When few trypanosomes are injected intraperitoneally, they may be disposed of by phagocytosis, and systemic infection may not occur. Phagocytosis within the circulating blood was never observed. Sections of tissues of rats killed at frequent intervals after intraperitoneal injections failed to reveal trypanosomes in organs prior to their appearance in the peripheral blood. Later the Kupffer cells of the liver and the endothelial cells of the spleen showed evidence of the phagocytosis of trypanosomes (nuclear débris). This occurred particularly in those rats surviving the longer periods.

PATHOLOGIC CHANGES IN RATS INFECTED WITH T. EQUIPERDUM

The pathologic changes in rats infected with T. equiperdum were briefly described by Andrews, Johnson and Dormal.[2] They noted cloudy swelling of the renal tubules, enlargement of the spleen, with congestion and evidences of lymphocytic degeneration, degenerative changes in the liver and hemorrhagic edema of the lungs with exudate of macrophages into the alveoli. They mentioned the presence of masses of agglutinated trypanosomes in the lung capillaries. In discussing the lethal factors in this disease, they stressed the importance of asphyxia, which leads to anoxemia and acidosis.

The pathologic changes in rats infected with T. equiperdum depend to some degree on the duration of the infection.

Methods.—In the course of the studies recorded here more than one hundred rats were observed at autopsy, and histologic sections of the organs of forty of these were prepared. In addition, a series of sixteen rats, each infected with 2,000 trypanosomes, was killed at twelve hour intervals for six days. Some rats in the series survived from ten to nineteen days, so that the progressive changes from the twelfth hour to the nineteenth day were available for study. To eliminate the effect of latent infection with B. muris, the trypanosomiasis in ten Wistar rats free from B. muris was also studied. No essential differences were noted in the pathologic changes induced by T. equiperdum in carriers of B. muris and rats free from this organism. Detailed protocols have been omitted. In all instances, bone marrow was examined. Sections were stained with hematoxylin and eosin, the May-Grünwald-Giemsa stain, Mallory's reticular stain and Mallory's iron stain. From this material an effort was made, when possible, to trace the pathogenesis of the disease. Trypanosomes undergo rapid postmortem autolysis, and they are difficult to see in sections, even though special care is taken with fixation of the tissues, and though sections are removed from the animal just before death, not after death.

At autopsy, a rat dead from an infection with T. equiperdum presents a striking splenomegaly. There is no change in the subcutaneous tissues, nor is there fluid in the peritoneum unless secondary anemia is severe. In such instances, slight effusions in the pleural cavities may occur.

Heart.—The myocardium shows cloudy swelling. If anemia is present at the time of death, fatty metamorphosis may be present. No inflammatory lesions are observed. The degree of fatty change is proportional to the anoxemia. In most instances it is absent.

Lungs.—The lungs show little change other than edema and congestion. Brownish-black pigment is found within large reticular elements (macrophages) in the perivascular tissue. This does not give the iron reaction. Large amounts of pigment are observed in the lumens of the vessels. Occasionally small accumulations of foam cells are seen in the alveoli. Occasionally trypanosomes are found in the capillaries of the lung. The veins are filled with trypanosome débris. Thrombi are not observed. Some veins contain many plasma-like cells and lymphocytes.

Spleen.—The spleen is greatly enlarged, deeply congested and friable. The surface is often covered with fine fibrinous strands. On section, the pulp oozes and is deep purple.

TABLE 4.—*The Relation of the Ratio of the Weight of the Spleen to That of the Body to the Duration of the Infection with T. Equiperdum in Albino Rats*

Number of Rats	Duration of Infection, Days	Weight of Spleen / Body Weight			
		Maximum Quotient	Minimum Quotient	Average Quotient	Mean Quotient
13	3	1.40	0.77	1.02	1.09
24	4	1.36	0.79	1.05	1.05
4	5	1.33	0.96	1.20	1.27
12	6	2.09	0.86	1.38	1.58
7	7	2.35	1.25	1.85	1.88
6	9	1.82	1.15	1.44	1.52
4	10-16	2.45	1.05	1.61	1.47
1	19	....	....	2.05	....
10	Controls	0.78	0.21	0.36	0.38

The size of the spleen varies with the duration of the infection. In rats infected with T. lewisi, progressive enlargement of the spleen with increase in the duration of the infection was observed by Marmorston, Perla and Vorzimer.[6] Reiner and Chao[12] noted a similar relationship in T. equiperdum. I was able to confirm these observations. A series of seventy adult rats, from 3 to 4 months of age, were given injections of varying numbers of trypanosomes (T. equiperdum); the spleens were weighed at death, and the ratio of the splenic weight to the body weight was determined. In control uninfected rats of the same age, the ratio of the splenic weight to the body weight was noted. The duration of the infection varied from three to nineteen days, depending on the number of trypanosomes injected. In rats in which the infection lasted three days the average ratio of the splenic weight to the body weight expressed in percentage was 1.02, and in infections of seven days' duration the average ratio was 1.85 per cent. At twelve days, it was 2.45 per cent (table 4). There is a progressive increase in the size of the spleen with the duration of the disease. This suggests the importance of the spleen in the defense mechanism to the disease.

Microscopic changes are noted as early as twelve hours after the injection of trypanosomes. The germinal centers of the follicles of the spleen show evidence

12. Reiner, L., and Chao, S. S.: Arch. internat. de pharmacodyn. et de thérap. **43**:209, 1932.

of increased activity, mitotic figures are present, and some increase in the lymphoblasts occurs. In the following days there is a progressive increase in the size of the follicles, and the lymphoblastic hyperplasia becomes more prominent. In addition, the cellularity of the pulp becomes more evident, the endothelial cells

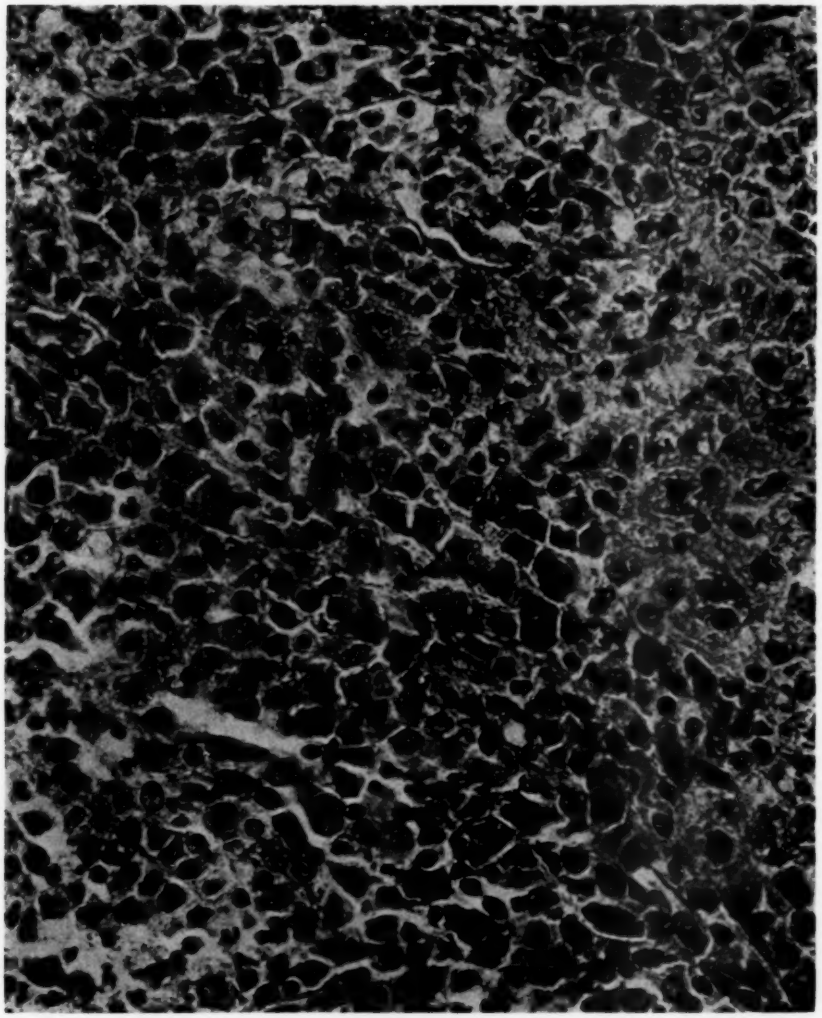

Fig. 1.—Spleen of a rat infected with T. equiperdum, showing large lymphoblastic cells and plasma-like cells in red pulp. Note the mitotic figures. The duration of the disease was four days. Hematoxylin and eosin stain; × 440.

swell, and there is evidence of erythrophagocytosis. At forty-eight hours the follicles are enlarged, and the number of small lymphocytes is decreased. The lymphoblasts are predominant. The outer zone of the follicles presents numerous pale-staining elements resembling closely packed reticular cells. A few plasma

cells appear in the red pulp, and there are scattered lymphocytes. The endothelial elements are swollen, and occasionally contain hemosiderin granules and blackish-brown pigment, which does not give the iron reaction.

At four and five days the follicles stand out prominently, owing to marked congestion of the pulp. The centers of the follicles are pale and contain numerous large lymphoblasts, large lymphocytes and some proliferation of reticular cells. There is evidence of focal cellular necrosis, and nuclear débris is seen within phagocytic reticular cells of the germinal centers. Occasional mitotic figures are seen. The number of mature small lymphocytes is markedly decreased. The edge of the follicle fades imperceptibly into the surrounding pulp tissue. About the outer zone of the follicle, many large lymphoblastic elements are seen. These contain mitotic figures. Occasional plasma cells are present. In some instances, many plasma cells are present about the periphery of the follicle and in the surrounding pulp tissue. Large numbers of lymphocytes are seen within the lumens of the larger blood vessels. Within the pulp, endothelial and reticular cells and macrophages are increased and are distended with ingested red blood cells. Many of these cells show degenerative changes. In places, areas of necrosis occur; the cellular elements are destroyed, but pigment and nuclear débris are present. Many endothelial cells contain fine granules of dark brown pigment in addition to hemosiderin granules.

In some animals dying on the fifth or sixth day, the splenic pulp contains numerous eosinophilic leukocytes. These are crowded about the smaller arterioles and venules. In sections of the spleen of animals surviving from ten to twelve days, in addition to the changes already noted, small lymphocytes are seen in greater number in the pulp than in the follicles. Intermediary forms between the large lymphoid cells and plasma-like cells are seen. The endothelial elements are swollen and fill the sinuses. Iron pigment and fine brown-black granules are scattered throughout the pulp and lie within distended endothelial cells. Iron pigment is found not only in the sinus endothelium of the red pulp but in reticular cells about the follicles. When stained with Mallory's iron stain, the pigment is seen to form a ring about the outer margin of the follicle. A second faintly staining ring is seen within the follicle between the intermediary zone of small lymphocytes and the outer zone of large pale mononuclear cells. The pigment here lies in oval cells that are arranged in an irregular syncytium.

Sheets of lymphoblastic cells occur in the pulp, and transitional forms from the proliferating reticular cells are apparently present.

Animals surviving sixteen and nineteen days show these changes to an even greater extent. The follicles are no longer clearly defined but merge irregularly. The small lymphocytes have left the follicles, and these consist almost entirely of large irregular lymphoblasts, many containing a more violet-tinged cytoplasm, such as is seen in plasma cells. The nuclei are large, slightly eccentric and somewhat irregular, and contain large masses of chromatin. Throughout the pulp are ectopic foci of lymphoblastic tissue containing clumps of small lymphocytes. The iron pigment has markedly diminished, but the blackish-brown pigment has strikingly increased.

The histologic changes in the spleen may be summarized as follows: There is progressive increase in the lymphoblastic elements in the follicles with decrease in the small lymphocytes. The size of the malpighian corpuscles is greatly increased. Extrafollicular foci of lymphoblastic and lymphocytic formation occur. Lymphoblastic hyper-

plasia is not associated with a corresponding increase in the production of lymphocytes, but apparently these give rise to many immature forms. In some instances, plasma cells occur in numbers, occasionally within the follicles and about the follicles. Reticular and endothelial cells increase in number and present evidence of active phagocytosis of red cells and of pigment. There is, however, an early exhaustion of these cells with evidence of necrosis. In some instances large numbers of eosinophils appear in the meshes of the pulp, close to small blood vessels. Iron pigment may be present in moderate abundance in animals dying within a few days after the initial infection, but it is apparently markedly decreased in animals surviving from ten to twelve days. There is, however, a progressive increase in blackish-brown melanin-like pigments, such as is seen in malaria.

Lymph Nodes.—The retroperitoneal lymph nodes and those in the mediastinum are enlarged early in the disease. Marked activity of the germinal centers occurs. There is an increase in the lymphoblasts of the follicles. Numerous plasma cells are present. The reticular cells and the endothelial cells of the sinuses are tremendously distended with nuclear débris. The hemolymph glands of the mediastinum show proliferation of the endothelial cells of the sinuses with erythrophagocytosis by these elements.

Liver.—The liver shows marked parenchymatous degeneration and congestion of the sinuses. The Kupffer cells are prominent, swollen and distended with ingested nuclear fragments and red blood cells. Many contain brownish-black, melanin-like pigment. The swollen Kupffer cells often distend the hepatic capillaries. They may contain lipoid droplets in abundance and chromatin fragments of ingested trypanosomes. In some areas there are small nodules of proliferated Kupffer cells. Focal necroses may occur. Larger veins occasionally contain antemortem thrombi filled with trypanosomes undergoing disintegration.

In some instances, periportal accumulations of small numbers of lymphocytes are seen. These occur about reticular elements and suggest lymphoblastic foci. Focal necrosis within these areas may occur. There is pericapillary edema throughout the liver. In instances associated with secondary anemia, the liver cells show varying degrees of fatty metamorphosis. In animals surviving sixteen and nineteen days, the liver presents a striking picture. Scattered through the liver are small nodules of cells. These occur within the lobules and bear no definite anatomic relationship to the portal spaces. They are composed largely of pale-staining cells with ill-defined cytoplasm and ovoid or round chromatin-poor vesicular nuclei. Many nodules contain small lymphoid elements and phagocytic mononuclear cells. Some of these nodules show evidence of necrosis. In some there is evidence of fibrotic change. These nodules resemble somewhat the "endothelial" nodules seen in typhoid. They may be interpreted as arising by proliferation of Kupffer cells.

Thymus.—This gland shows no evidence of lymphoblastic proliferation such as is seen in the lymph nodes and spleen.

Suprarenal Gland.—These are enlarged and edematous, and the cells of the cortex show marked cloudy swelling.

Kidneys.—There is a severe degeneration of the tubules. In animals surviving the longer periods the epithelium may show necrobiotic changes. The

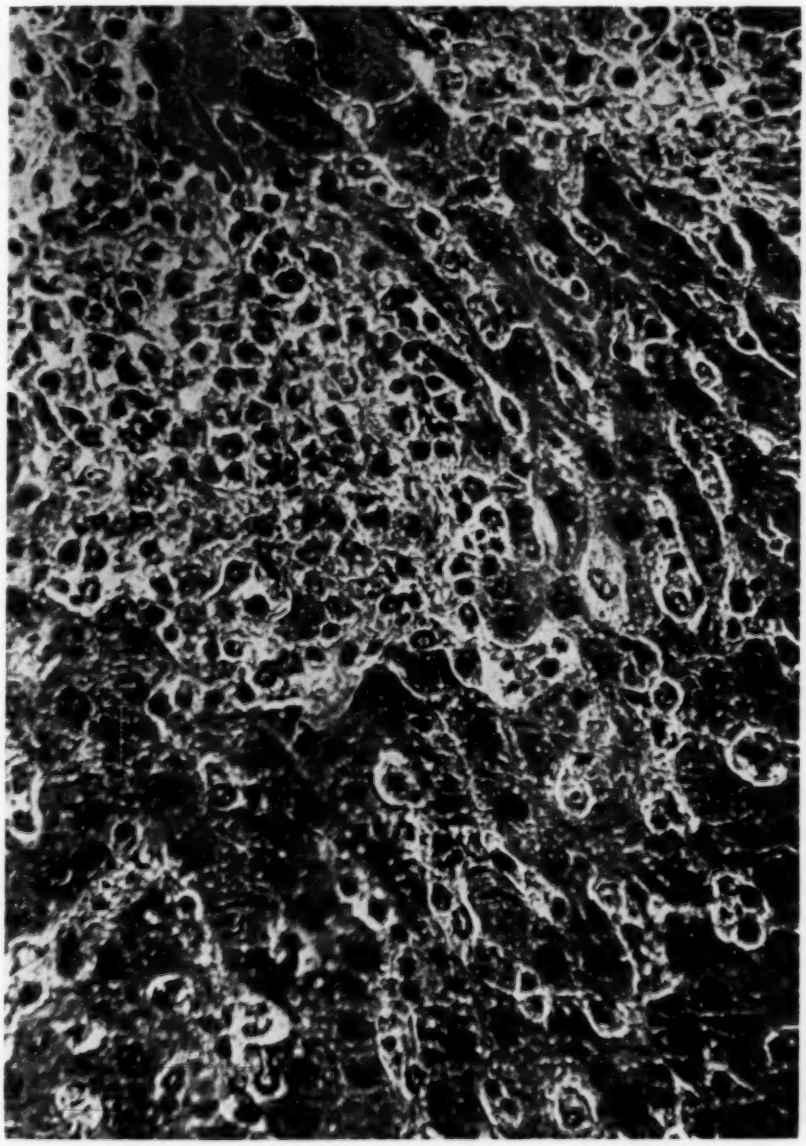

Fig. 2.—Liver of rat infected with T. equiperdum, showing nodule of Kupffer-like cells. The duration of the infection was nineteen days. Hematoxylin and eosin stain; × 440.

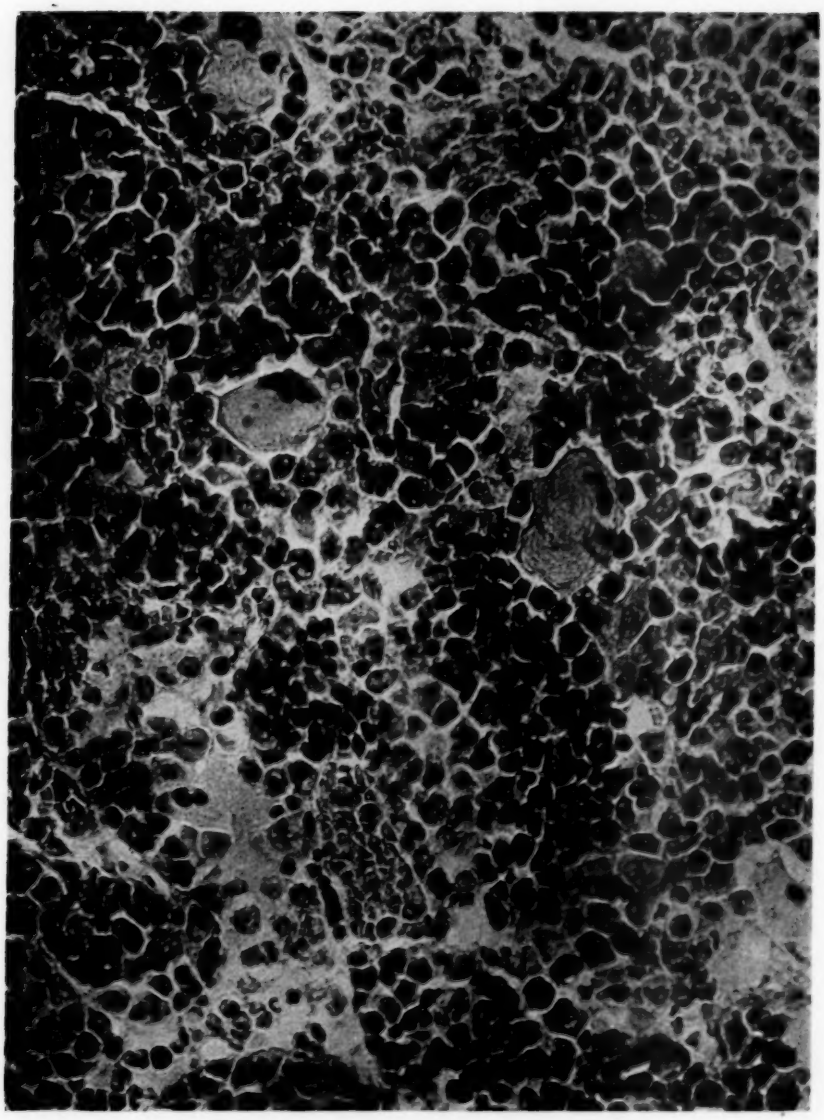

Fig. 3.—Bone marrow of a rat infected with T. equiperdum, showing increase in megakaryocytes and hemocytoblasts. (Section showed an increase in eosinophilic myelocytes.) The duration of infection was nine days. Hematoxylin and eosin stain; × 440.

glomeruli are shrunken, and the capillary loops are collapsed. An anemia of the tufts is present.

Bone Marrow.—The marrow of the femur appears more prominently grayish red than in the normal animals. Within from twelve to twenty-four hours, the eosinophilic leukocytes and myelocytes are increased. Mast cells that are only occasionally observed in normal marrow are present in prominent numbers. After the second or third day there is an increase in hemocytoblastic cells, and the proliferation of eosinophilic myelocytes and leukocytes becomes more pronounced. The megakaryocytes are increased in size and number. Polychromatic erythroblasts are present in greater numbers than normally, some undergoing mitoses. In general, there is a definite hyperplasia of all elements of erythropoiesis and myelopoiesis.

COMMENT

The disease affects the macrophage tissue of the body. The striking activity of the endothelial and reticular cells of the spleen leads to exhaustion and necrosis of these elements. In the liver the Kupffer cells are markedly phagocytic and contain chromatin débris from ingested trypanosomes. Many contain red blood cells. Death of these cells leads to focal necroses. In infections lasting longer periods, nodules of proliferated Kupffer cells occur. In the lymph nodes the endothelial elements are stimulated to increased phagocytic activity. Significant changes in the spleen and the macrophage system in general suggest the important rôle of these cells in the mechanism of resistance to infection with T. equiperdum. The importance of the macrophage system has been clearly indicated in other trypanosomal diseases (as in kala-azar [13]), and is discussed in detail by Linton.[14] Further evidence of the importance of the macrophage in resistance to this infection is afforded by the high content of mononuclear phagocytes in the peritoneal exudate immediately following the injection of trypanosomes.

In addition, however, to these changes there is a pronounced stimulation of the lymphoblastic tissue of the spleen and lymph nodes. Similar findings were reported in the careful studies of Hu [15] and Hu and Ch'in [16] of an infection of rats with Trypanosoma brucei. They noted marked and rapid lymphoblastic hyperplasia in the spleen and lymph nodes, with increase in the number of plasma cells. They described transitional forms between lymphoblasts and plasma cells as determined by Mallory's eosin-methylene blue stain and by supravital preparations. The increase in lymphoblastic activity in the spleen and lymph nodes is reflected in the progressive relative increase of lymphocytes and a high percentage of lymphoblasts in the circulating blood.

Another interesting phase of the disease is the eosinophilic response. The prominent outpouring of eosinophils within from ten to twenty

13. Hu, C. H., and Cash, J. R.: Proc. Soc. Exper. Biol. & Med. **24**:469, 1927.
14. Linton, R. W.: Arch. Path. **8**:488, 1929.
15. Hu, C. H.; Am. J. Path. **10**:29, 1934; Nat. M. J. China **17**:435, 1931.
16. Hu, C. H., and Ch'in, K. Y.: Am. J. Path. **10**:43, 1934.

minutes after the injection of trypanosomes into the peritoneal cavity is a very striking phenomenon. With progression of the disease a moderate increase in eosinophilic leukocytes is noted in the circulating blood. In some animals, about the fifth and sixth day the splenic pulp may be infiltrated with eosinophilic leukocytes. The bone marrow shows large numbers of eosinophilic myelocytes and leukocytes. The significance of this eosinophilia is not clear. It may be analogous to the eosinophilia associated with other parasitic diseases.

There are several distinct elements in the disease that are responsible for the pathologic changes: 1. The presence of large numbers of parasites in the blood with their continued destruction and the release of foreign particulate matter into the circulation stimulates the phagocytic activity of the macrophage tissue, primarily of the spleen, liver and lymph nodes. 2. The production of hemolytic toxins released in the metabolism of the trypanosomes results in a destruction of red cells, and this further necessitates the disposal of débris by cells of the macrophage system. In severe and prolonged infections, this hemolytic effect leads to secondary anemia, with pathologic changes resulting from marked anoxemia of the tissues and varying degrees of hyperplasia of erythropoietic tissue in the bone marrow. 3. The unusual response of the lymphoblastic tissue is probably the effect of toxemia and may represent a futile effort on the part of the lymphoid tissue to produce antibodies. It is generally conceded that the lymphoid tissue is important in the production of antibodies. However, in this infection neither reproduction-inhibitive nor trypanolytic antibodies are demonstrable.

The immediate cause of death has been thoroughly analyzed by several investigators, particularly Andrews, Johnson and Dormal,[2] Linton[3] and Linton and Poindexter.[17] Within the last twenty-four hours of life there is marked hypoglycemia. Associated with this is a progressive exhaustion of the hepatic glycogen. An acidosis develops early and increases in severity. Terminally there is a rise in the nonprotein nitrogen of the blood.

SUMMARY

The duration of infection with T. equiperdum in rats varies with the number of trypanosomes injected. The duration of the disease varies from three days if overwhelming numbers of trypanosomes are injected to a period of from ten to nineteen days if 2,000 trypanosomes are injected. With the injection of fewer trypanosomes many rats of the stock used in this study escape infection.

There is a relative lymphocytosis with little variation in the total white cell count.

17. Linton, R. W., and Poindexter, H. A.: J. Exper. Med. **54**:669, 1931.

A secondary hemolytic anemia develops in rats surviving five or six days. This is unassociated with B. muris and occurs in rats that are not carriers of this latent infection.

An anemia may be induced in normal young rats by the injection of cell-free filtrates of the diluted blood of rats infected with T. equiperdum. This anemia is not transferable beyond this single passage and is probably due to a hemolytic toxin elaborated by the trypanosomes.

The iron content in the liver, as determined by chemical methods, increases in infection with T. equiperdum. The copper content of the liver is unaffected. The concentration of iron in the spleen is definitely less than that in normal uninfected rats. There is a striking decrease in copper in the spleen.

The inflammatory response to T. equiperdum injected intraperitoneally is characterized by a marked accumulation of mononuclear phagocytes (macrophages), eosinophilic leukocytes and mast cells.

The pathologic changes in rats infected with T. equiperdum occur primarily in the spleen, liver, lymph nodes and bone marrow. The changes consist in hyperplasia of the Kupffer cells of the liver, the endothelial cells of the lymph nodes and the endothelial and reticular cells of the spleen, with evidence of increased phagocytic activity of these cells. Focal necroses occur in the liver and spleen. There is a marked lymphoblastic proliferation of the follicles of the spleen and lymph nodes, with the appearance of ectopic foci of lymphoid cell formation in the red pulp of the spleen. Plasma cells increase in number within the splenic red pulp. A marked increase in eosinophilic myelocytes and leukocytes is noted in the marrow and may occur in the spleen.

The pathologic changes are essentially the same in rats that are carriers of B. muris and in rats that are free from this latent infection.

QUANTITATIVE STUDY OF MITOCHONDRIA IN VARIOUS GRADES OF SQUAMOUS CELL CARCINOMA

ZOLA K. COOPER, PH.D.
AND
M. G. SEELIG, M.D.
ST. LOUIS

REVIEW OF THE LITERATURE

The histologic grading of malignant tumors has assumed increasing importance, especially among American workers, during the past decade. Broders [1] in 1920 was the first to work out a system for dividing squamous cell carcinoma into four grades on the basis of the degree of cellular differentiation. Martzloff [2] devised a similar method based on cell types. In 1924 MacCarty,[3] taking into consideration the additional factors of the degree of lymphocytic infiltration, fibrosis and hyalinization, developed a new classification. Perhaps the most elaborate system of grading was devised by Hueper [4] and his co-workers, who, on the basis of twenty histologic factors to which they assigned numerical values (the malignogram), obtained a figure representing the degree of malignancy—the "malignancy index." The various later attempts to grade tumors made by different workers were carefully reviewed by Plaut [5] and Hueper.[6]

One of the most significant results of these studies has been the tendency of surgeons to regulate the application of therapy according to the grade of the tumor. In addition, some investigators have attempted to show a definite relationship between radiosensitivity and the grade of the tumor (Quick and Cutler [7]). Even now, however, many of the factors which form the basis for grading are clinical rather than histologic, and the histologic criteria for grading have not been absolutely established.

Cytologic studies have been comparatively few. Consequently, the careful examination of any of the finer cell elements which might serve as a further basis for the grading of carcinoma seems to be of value.

From the Research Department of the Barnard Free Skin and Cancer Hospital.

1. Broders, A. C.: J. A. M. A. **74**:656, 1920.
2. Martzloff, K. H.: Bull. Johns Hopkins Hosp. **34**:141, 1923.
3. MacCarty, W. C.: Ann. Clin. Med. **2**:244, 1924.
4. Hueper, W. C.: Surg., Gynec. & Obst. **47**:502, 1928.
5. Plaut, A.: Arch. Path. **3**:240, 1927.
6. Hueper, W. C.: Arch. f. klin. Chir. **159**:200, 1930.
7. Quick, D., and Cutler, M.: Surg., Gynec. & Obst. **45**:320, 1927.

The present paper, a quantitative cytologic study of the mitochondria of squamous cell carcinoma, was undertaken to determine the relationship of mitochondria to the grading of malignancy. Other investigators have studied mitochondria in tumor cells, but these studies have been neither quantitative nor related to the grading of tumors.

Mitochondria are rod-shaped or filamentous cell organs of a complex phospholipid nature, which are found almost universally in the cytoplasm of both plant and animal cells. They can be demonstrated in the living, unstained cell. They are extremely soluble, however, in alcohol, acetic acid and other similar reagents and can be demonstrated in paraffin sections only after the use of special fixatives. The mitochondria in individual cells are usually distributed without definite arrangement throughout the cytoplasm. In different tissues they vary in amount, abundant mitochondria being associated with intense protoplasmic activity. The number of mitochondria decreases with cellular senescence. A relationship also seems to exist between the number of mitochondria and the amount of fat that is present. Cowdry [8] said:

> Where there are few mitochondria, there is often much fat and vice versa. Decreased oxidation favors its deposition and increased oxidation hastens its elimination, which suggests at once the existence of some connection between the amount of mitochondria and the rate of oxidation; and their abundance in the more active stages of the life of the cell when protoplasmic respiration is rapid, points to the same tentative conclusion.

Biologic chemists (Bloor [9]) have also shown that the phospholipid content of tissues increases with increased metabolism. Bullard [10] reported that the mitochondria are more than twice as abundant in heart muscle as in skeletal muscle, thus supporting the chemical findings of Erlandsen [11] and Bloor [9] that heart muscle has more than twice as much phospholipid as skeletal muscle. Bierich, Detzel and Lang [12] showed that tumor tissue has a relatively higher phospholipid content than normal tissue. Bloor [13] went a step farther and showed that more malignant tumors (cancer as compared with fibromyoma, colloid adenoma and fibrosarcoma) have a higher phospholipid content.

Since mitochondria are phospholipid in nature and are more numerous in more active cells, it was thought that they might be found to vary quantitatively in malignant tumors. The higher grades of carcinoma are considered to be both more active and more malignant. Conse-

8. Cowdry, E. V.: General Cytology, Chicago, University of Chicago Press, 1924, p. 313.

9. Bloor, W. R.: J. Biol. Chem. **68**:33, 1926; **72**:327, 1927.

10. Bullard, H. H.: Am. J. Anat. **19**:1, 1916.

11. Erlandsen, A.: Ztschr. f. physiol. Chem. **51**:71, 1907.

12. Bierich, R.; Detzel, A., and Lang, A.: Ztschr. f. physiol. Chem. **201**:157, 1931.

13. Yasuda, M., and Bloor, W. R.: J. Clin. Investigation **11**:677, 1932.

quently, we attempted to determine whether the mitochondrial content of the cells of the different grades of tumors might serve as an index of malignancy. A quantitative study of the mitochondria in the various grades of squamous cell carcinoma was undertaken.

Quantitative studies of mitochondria, even in normal tissues, have been few. Cowdry and Covell [14] determined a mitochondria-cytoplasmic ratio for the cells of the normal renal tubules, and du Noüy and Cowdry,[15] for the cells of the normal pancreas. No similar studies have been made on malignant tissue. Therefore, the present study is an attempt to determine the mitochondria-cytoplasmic ratio for tumor cells as compared with normal cells of the same tissue, and to determine the mitochondria-cytoplasmic ratio in the different grades of squamous cell carcinoma. The method followed for the determination of the mitochondria-cytoplasmic ratio was that of Cowdry and Covell.[14]

MATERIAL AND METHODS

The tissue used for these studies was obtained in the operating room from patients with squamous cell carcinoma of the lip, tongue, jaw, esophagus, buccal membrane, cheek, temple, neck, palate, cervix and penis and, in one case, from lymph node metastases (primary carcinoma of the esophagus). The material was taken directly from the operating room and fixed immediately in Regaud's fluid.[16] After dehydration the tissue was embedded in paraffin and sections were cut 2 microns in thickness. The sections were stained with acid fuchsin and methyl green. Whenever it was surgically possible, comparable pieces of normal tissue were taken from the same patient at the same time and treated similarly. In the case of the carcinomatous tissue one half of the block was fixed in a dilute solution of formaldehyde U. S. P. (1:10), dehydrated and embedded in paraffin. After sections had been made, the slides were stained with the routine hematoxylin-eosin stain and submitted to the pathologist of the Barnard Free Skin and Cancer Hospital, Dr. Louis H. Jorstad, for independent grading, as a check against our determination of grade.

For the study of the mitochondria only typical cells cut squarely through the center were chosen. Camera lucida drawings of from ten to fifteen cells for each case of carcinoma and for each control slide of normal tissue were made at table level with an optical combination yielding a magnification of 3,200 diameters. Special care was taken to draw the mitochondria with accuracy. The surface area of each cell and of its nucleus was computed by means of a planimeter. The area of cytoplasm was then calculated by subtracting the area of the nucleus from the total area of the cell. The area of cytoplasm was then divided by the magnification squared ($3{,}200^2$) and multiplied by the thickness of the section to obtain the volume of cytoplasm in cubic microns. The total mitochondrial surface was then calculated by measuring on the drawings with a pair of dividers the total length of the mitochondria in each cell. A correction was made, of course, for the magnification. The mitochondria in all the cells of squamous epithelium examined (both malignant and nonmalignant) were found to be cylindrical rods. The diameter of

14. Cowdry, E. V., and Covell, W. P.: Anat. Rec. **36**:349, 1927.

15. Du Noüy, P. L., and Cowdry, E. V.: Anat. Rec. **34**:313, 1927.

16. Regaud's fluid is made up of 2.5 per cent solution of potassium dichromate, 4 parts, and solution of neutral formaldehyde, U. S. P., 1 part.

these rods was quite uniform throughout. Consequently, the mean diameter of the mitochondria was obtained by direct measurement with an ocular micrometer on one hundred cells and was found to be 0.55 micron. The total surface area of the mitochondria in each cell was then computed as for a cylinder.

A mitochondria-cytoplasmic ratio was then obtained according to the method of Cowdry and Covell [14] by dividing the total mitochondrial surface in square microns by the cytoplasmic volume in cubic microns and multiplying by 100. This figure represents the mitochondrial surface per hundred cubic microns of cytoplasm.

TABLE 1.—*The Mean Mitochondria-Cytoplasmic Ratios Computed for Nine Squamous Cell Carcinomas (Grades 1 to 3)*

Location	Grade	Mitochondria-Cytoplasmic Ratio
Temple	1	5.25
Lip	2	3.86
Tongue (2 cases)	2	3.69
Esophagus	2	6.87
Esophagus (metastatic)	2	4.95
Buccal membrane	3	4.05
Neck	3	4.94
Cheek	3	5.78

TABLE 2.—*The Mean Mitochondria-Cytoplasmic Ratios Computed for Squamous Cell Carcinomas (Grades 1 to 3)*

Grade of Carcinoma	Mitochondria-Cytoplasmic Ratio
1	5.25
2	4.55
3	4.91

TABLE 3.—*The Mitochondria-Cytoplasmic Ratios for Carcinomatous and for Normal Tissue Obtained from Four Patients*

Tissue	Mitochondria-Cytoplasmic Ratio	
	Carcinomatous Tissue	Normal Tissue
Esophagus	6.87	9.33
Esophagus (metastatic)	4.95	9.33
Tongue	3.81	3.58
Lip	3.86	3.55
Mean values	4.75	6.50

EXPERIMENTAL OBSERVATIONS

Squamous cell carcinomas of grades 1, 2 and 3 (Broders' classification) were studied. No grade 4 squamous cell carcinomas were obtained from the material available at the time. The carcinomas studied were from the temple, lip, tongue, esophagus, palate, jaw, buccal membrane, neck, cheek, cervix and penis. Fifteen cases in all were studied. Table 1 presents the mean mitochondria-cytoplasmic ratios in nine of these cases.

In six additional cases (cervix, three; palate, one; jaw, one; penis, one) not presented in the table, mitochondria could not be demonstrated in enough cells to make the counts of statistical significance. All of these cases were instances of grade 1 or grade 2 carcinoma in which a high degree of keratinization was present. In the keratinized cells mitochondria were not found. This change in the distribution of mitochondria is not especially characteristic of cancer cells but occurs wherever keratinization takes place. This observation is in keeping with that of Ludford [17] and with the theory that mitochondria are decreased in number in senescent cells.

Table 2 presents the mean mitochondria-cytoplasmic ratios for the three grades of squamous cell carcinoma included in this study.

Control tissue for the estimation of the mitochondria-cytoplasmic ratio in normal cells could not be obtained in every case because of surgical difficulties. Table 3 presents the mitochondria-cytoplasmic ratio in those cases in which both normal and carcinomatous tissue could be obtained from the same patient.

COMMENT

From the results two observations seem noteworthy:

1. No significant differences are apparent in the mitochondria-cytoplasmic ratios of the normal and of the cancerous tissue. Thus, although the phospholipid content of malignant tissue is greater than that of normal tissue, according to Bloor [13] and Bierich, Detzel and Lang,[12] this difference cannot be demonstrated morphologically by any quantitative change in the mitochondria of cancer cells. In fact, the mean mitochondria-cytoplasmic ratio, i. e., the mitochondrial surface per hundred cubic microns of cytoplasm, is somewhat greater for the normal tissue (6.5) than for the cancer tissue (4.75).

2. The mean mitochondria-cytoplasmic ratios for the three grades of squamous cell carcinoma studied are not significantly different. Less difference was found in the mean mitochondria-cytoplasmic ratios for each of the three grades of squamous cell carcinoma than was observed between the ratios for normal and those for carcinomatous tissue. In some carcinomas of grade 1 or 2 in which keratinization was marked, almost complete disappearance of the mitochondria was noted. In other grade 1 carcinomas, however, the mitochondria were more numerous than in tumors of grade 3. Consequently, a quantitative estimation of the mitochondria in squamous cell carcinoma does not form any basis for grading.

17. Ludford, R. J.: J. Roy. Micr. Soc., 1925, pt. 3, p. 249.

CONCLUSIONS

1. The mitochondria-cytoplasmic ratio is greater for normal tissue (6.5) than for squamous cell carcinomatous tissue (4.75).

2. No significant differences were found in the mitochondria-cytoplasmic ratios for the three grades of squamous cell carcinoma studied.

3. The quantity of mitochondria present in cancer cells is not a histologic basis for grading.

CHOLESTEROL-INDUCED ATHEROSCLEROSIS

ITS PREVENTION IN RABBITS BY THE FEEDING OF AN ORGANIC IODINE COMPOUND

IRVINE H. PAGE, M.D.

AND

WILLIAM G. BERNHARD, M.D.

NEW YORK

In 1908, it was demonstrated by Ignatowski [1] and Saltykow [2] that the feeding of rabbits with foods such as meat, milk and eggs resulted in thickening of the intima of the aorta. Stukkeu [3] and Wacker and Hueck,[4] but especially Anitschkow,[5] showed definitely that the atherosclerosis was due, not to protein, but to the cholesterol which was ingested. Since that time Anitschkow has championed the view that atherosclerosis produced by cholesterol in rabbits represents the counterpart of arteriosclerosis in man.[6]

Although the morbid changes in the arteries have been extensively studied, the chemical alterations in the blood have received scant attention. The amount both of cholesterol and of fatty acids is increased in the blood following ingestion of cholesterol dissolved in oil. Schönheimer [7] has shown that the lipids which are deposited in the human aorta are of such composition as to suggest that they exist preformed in the blood and that infiltration and deposition occur without change in composition. Phosphatides, however, occur in the aorta in much smaller amounts than in the plasma.

It has seemed logical to many investigators that only continued lipemia may result in atherosclerosis. This opinion is based on the view that lipemic plasma, which is supposed to be supersaturated with lipids,

---

From the Hospital of the Rockefeller Institute for Medical Research.

1. Ignatowsky, A.: Ber. d. mil. med. Akad., St. Petersburg **16**:174, 1908; Virchows Arch. f. path. Anat. **198**:248, 1909.

2. Saltykow, S.: Centralbl. f. allg. Path. u. path. Anat. **19**:321, 1908.

3. Stukkeu, N. V.: Dissertation, Saint Petersburg, 1910; Centralbl. f. allg. Path. u. path. Anat. **23**:910, 1912.

4. Wacker, L., and Hueck, W.: München. med. Wchnschr. **60**:2097, 1913.

5. Anitschkow, N.: Beitr. z. path. Anat. u. z. allg. Path. **56**:379, 1913; **57**: 201, 1914; **59**:306, 1914.

6. The arguments for and against the view have recently been summarized in Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933.

7. Schönheimer, R.: Ztschr. f. physiol. Chem. **160**:61, 1926; **177**:143, 1928.

infiltrates the walls of the vessels and there deposits some of its excess fatty material. Since cholesterol tends to be deposited at points in the vessels where the blood pressure is greatest, it has been recognized that increased pressure also favors the deposition of cholesterol. Clinical experience tends to support the belief that both lipemia and increased blood pressure lead to atherosclerosis. Diabetes, nephrosis, the Hand-Schüller-Christian syndrome and possibly myxedema are distinguished by the frequency with which they are accompanied by atherosclerotic changes.

Since it is admitted that lipemia contributes to the deposition of lipids in the walls of the vessels, two questions arise: First, why do strictly localized atherosclerotic plaques occur as in coronary sclerosis? Second, may lipemia persist without the formation of atherosclerotic plaques? Through the work of Murata and Kataoka,[8] Liebig,[9] Turner[10] and Friedland[11] it has become evident that administration of thyroid substance or of iodides prevents the deposition of cholesterol when the latter substance is fed to rabbits. Whether the effectiveness of iodides is due to the prevention of lipemia or to the prevention of the deposition of lipids has not been determined. Should it be found that lipemia may exist without the appearance of atherosclerosis in iodine-fed rabbits, it seems reasonable to assume that in addition to lipemia and to pressure, a third factor, namely, the state of tissue metabolism, is active in the morbid process leading to the appearance of atherosclerosis. The following experiment dealt with these points.

METHOD

Male and female rabbits (hybrids of blue English and lilac strains) bred at the Rockefeller Institute were employed. The ages ranged from 5½ to 8 months and the weights from 1,800 to 2,700 Gm. The diet consisted of cabbage, clover hay and a mixture of oats with pellets containing a mixture of vitamins and minerals, including very small amounts of vegetable fat.

Cholesterol was dissolved in warm olive oil to make a 5 per cent solution, and the preparation was administered from a 10 cc. syringe through a soft rubber tube gently inserted into the proximal portion of the esophagus. Under this treatment inhalation pneumonia developed in only two of twenty-four rabbits during the course of several months' feeding. The animals were fed 200 mg. of cholesterol daily on six days of the week; in spite of this large amount there was no loss of appetite. The method had the advantage of allowing accurate dosage. The duration of the feeding varied from one hundred and nine to one hundred and eighty days.

---

8. Murata, M., and Kataoka, S.: Verhandl. d. Jap. path. Gesellsch. **7**:27, 1917.
9. Liebig, H.: Arch. f. exper. Path. u. Pharmakol. **159**:265, 1930; **175**:409, 1934.
10. Turner, K. B.: J. Exper. Med. **58**:115, 1933.
11. Friedland, I. B.: Ztschr. f. d. ges. exper. Med. **87**:683, 1933.

The di-iodide of ricinsterolic acid, containing 15.56 per cent of iodine according to our analysis,[12] was employed to prevent the production of atherosclerosis. This substance was used because Wottschall [13] found that it did not irritate the stomach and that the iodine remained in the blood stream longer than it did with the other preparations of iodine which were tested. According to Turner, however, other iodine compounds appear equally effective in preventing atherosclerosis in rabbits.

TABLE 1.—*Effect of Feeding of Cholesterol and Cholesterol and an Organic Iodine Compound on the Production of Atherosclerosis in Two Series of Rabbits*

Rabbit	Sex	Weight		Duration of Experiment, Days	Intake of Cholesterol, Gm.	Intake of Di-Iodide of Ricinsterolic Acid, Gm.	Degree of Atherosclerosis of Aorta
		At Beginning, Gm.	At End, Gm.				
Series of Rabbits Fed Cholesterol in Olive Oil							
13 A	F	1,800	2,100	110	16.8	.....	Moderate
14 A	F	2,300	2,620	163	27.8	.....	Very marked
16 A	F	2,420	2,080	179	30.6	.....	Marked
15 A	F	2,010	2,140	180	30.8	.....	Very marked
22 A	M	2,440	2,140	180	30.8	.....	Moderate
23 A	M	2,250	1,960	180	30.8	.....	Moderate
Series of Rabbits Fed Cholesterol-Olive Oil and an Organic Iodine Compound							
24 B	M	1,900	1,940	109	17.20	12.00	None
20 B	M	2,040	1,730	132	18.80	13.08	Very slight
25 B	M	2,800	2,140	139	23.80	26.40	Very slight
19 B	M	2,750	2,240	165	28.32	23.48	Very slight
17 B	F	2,400	2,200	171	29.20	24.98	Slight
18 B	F	2,300	2,130	179	30.60	27.38	Slight

TABLE 2.—*Average Content of Lipids per Hundred Cubic Centimeters of Plasma in Normal Rabbits and in Rabbits Fed Cholesterol or Cholesterol and an Organic Iodine Compound*

Series of Rabbits	Total Lipid Carbon, Mg.	Total Lipids as Lipid Carbon × 1.3, Mg.	Total Cholesterol, Mg.	Free Cholesterol, Mg.	Esterified Cholesterol, Mg.	Lipid Nitrogen, Mg.	Lipid Phosphorus, Mg.	Phosphatides Estimated as Lipid Phosphorus, × 23.5, Mg.	Cephalin Estimated as Lipid Amino Nitrogen, Mg.	Cephalin Estimated as Lipid Amino Nitrogen, × 47.5, Mg.
Receiving regular diet.....	212	275	72	26	46	4.8	5	82	2.8	150
Receiving cholesterol	2,232	2,902	1,435	356	1,079	16.2	22.4	526	6.7	358
Receiving cholesterol and organic iodine compound.....	2,901	3,771	1,783	547	1,236	18.3	26.1	613	8.8	471

Samples of blood for the estimation of lipids were drawn from a vein of the ear into an anticoagulant from dog liver after twenty-four hours' fasting. The method used for the analysis of the lipids was that of Kirk, Page and Van Slyke.[14] As far as possible, in each series analyses were made on blood drawn from the animals which had had comparable treatment.

12. The pulverized tablets were analyzed by fusing with sodium carbonate, precipitating the iodide with silver nitrate and weighing the silver iodide.

13. Wottschall, B.: Arch. f. exper. Path. u. Pharmakol. **54**:123, 1927.

14. Kirk, E.; Page, I. H., and Van Slyke, D. D.: J. Biol. Chem. **106**:203, 1934.

RESULTS

The duration of the experiment and the amount of cholesterol fed the animals in the two series were comparable (table 1).

The animals fed cholesterol and olive oil either gained or lost a small amount of weight, while those fed cholesterol, olive oil and the di-iodide of ricinsterolic acid lost weight. All of the six rabbits fed cholesterol exhibited an extensive deposition of cholesterol in the intima of the aorta and large amounts of fat in the liver. On the other hand,

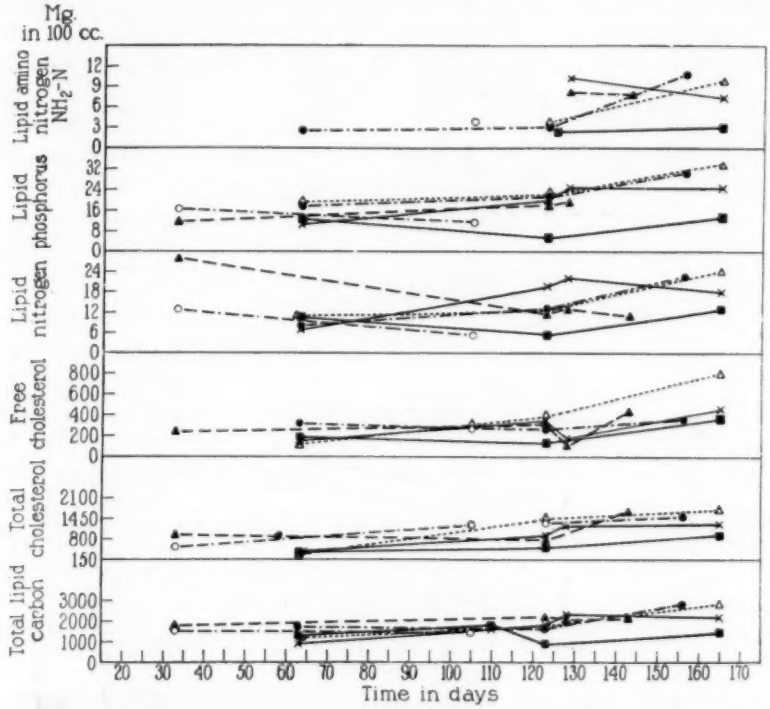

Chart 1.—Average content of lipids, expressed in milligrams per hundred cubic centimeters of plasma, in a series of six rabbits receiving cholesterol in olive oil. The values for rabbit 13 A are shown by long and short dashes and hollow circles; for rabbit 14 A, by long dashes and solid triangles; for rabbit 15 A, by a solid line and solid squares; for rabbit 16 A, by long and short dashes and solid circles; for rabbit 22 A, by a solid line and crosses, and for rabbit 23 A by short dashes and hollow triangles.

all of the animals fed the organic iodine compound in addition to cholesterol showed either no deposition of cholesterol in the intima or, at most, slight morbid changes in the aorta or in the liver.

Analysis of the plasma for the lipid content showed that the amount of lipid was low in the normal rabbits (table 2). Feeding cholesterol

in oil caused an enormous increase in the amounts of all lipid fractions, especially the total, esterified and free cholesterol. The amounts of phosphatides and cephalin were elevated, but the percentage of increase was not so great as that of the total fat or of the total cholesterol. The plasma of animals fed the di-iodide of ricinsterolic acid in addition to cholesterol in oil throughout the experiment contained even more lipids than that of the animals fed only cholesterol in oil.

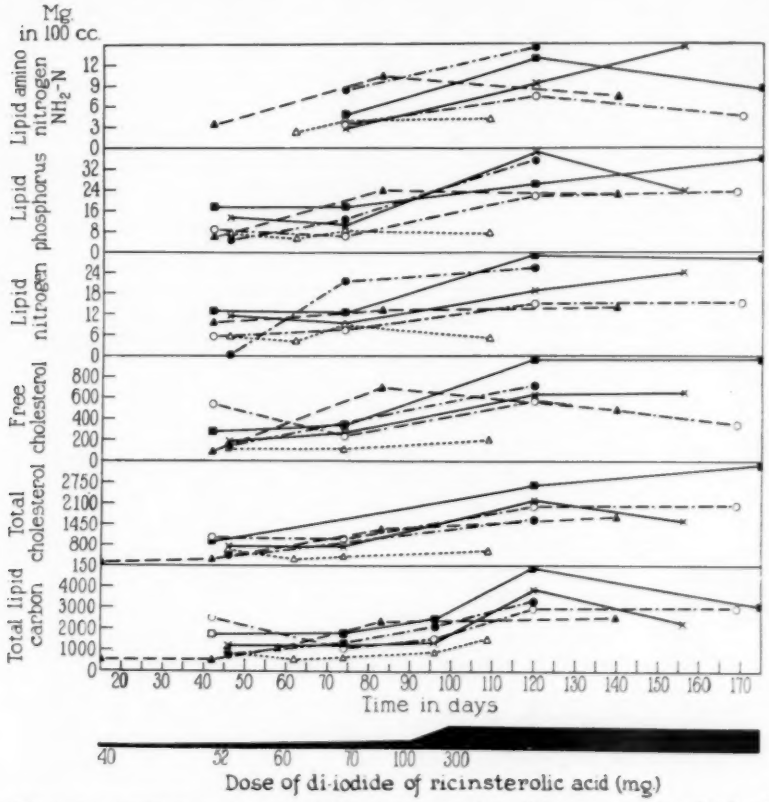

Chart 2.—Average content of lipids, expressed in milligrams per hundred cubic centimeters of plasma, in a series of six rabbits receiving cholesterol in olive oil and the di-iodide of ricinsterolic acid. The values for rabbit 17 B are shown by long and short dashes and hollow circles; for rabbit 18 B, by a solid line and solid squares; for rabbit 19 B, by a solid line and crosses; for rabbit 20 B, by long and short dashes and solid circles; for rabbit 24 B, by short dashes and hollow triangles, and for rabbit 25 B, by long dashes and solid triangles.

COMMENT

Murata and Kataoka [8] appear to have been the first to suggest that preparations of iodine prevent the deposition of cholesterol in the arteries when the latter substance is fed to rabbits. They did not, however,

present their experiments in detail. This work has been elaborated and confirmed by Liebig [9] in 1930, Seel and Creuzberg,[15] Turner [10] and Friedland.[11] Turner [10] has in addition shown that thyroxin is less active than whole thyroid gland and that potassium iodide is also effective. Potassium chloride and potassium bromide exerted no protective action. When the thyroid gland was removed, potassium iodide failed to prevent the deposition of cholesterol (Turner and Khayat [16]).

We have observed that when lipemia is induced by feeding olive oil and cholesterol there is a rise not only in the neutral fat and the cholesterol content of the blood, but also in the amounts of lipid amino-nitrogen (partly cephalin), total lipid nitrogen and lipid phosphorus (largely phosphatides). Compared with lipemia observed in patients suffering from the nephrotic phase of Bright's disease, artificially induced lipemia in rabbits differs somewhat in that the amounts of cholesterol and neutral fat are elevated to a proportionately greater extent than are those of the other lipid fractions. Lipemia in Bright's disease is usually characterized by an elevation in the amounts of total lipids, total cholesterol, esterified cholesterol, lipid nitrogen, lipid amino-nitrogen and lipid phosphorus in about the same proportion for each fraction (Page, Kirk and Van Slyke [17]).

Feeding the di-iodide of ricinsterolic acid with cholesterol in oil not only does not prevent lipemia but appears to increase it. Throughout the experiment the animals receiving this substance exhibited higher values for all of the lipid fractions than did those receiving cholesterol in oil alone. Yet the deposition of cholesterol in the arteries or in other organs was minimal. We interpret this to mean that when the metabolism of the tissues of rabbits is altered by the administration of the di-iodide of ricinsterolic acid, deposition even from the lipemic plasma may be hindered. If the state of metabolism of tissues such as the walls of the arteries is an important factor in determining whether lipids will be deposited, it is understandable why atherosclerosis is a focal and not a general disease.

CONCLUSIONS

In confirmation of the work of others it has been found that administration of an organic iodine compound to rabbits receiving cholesterol dissolved in olive oil prevents the appearance of atherosclerosis which normally follows the administration of cholesterol and olive oil alone.

---

15. Seel, H., and Cruezberg, G.: Arch. f. exper. Path. u. Pharmakol. **161**:674, 1931.

16. Turner, K. B., and Khayat, G. B.: J. Exper. Med. **58**:127, 1933.

17. Page, I. H.; Kirk, E., and Van Slyke, D. D.: J. Clin. Investigation, to be published.

Persistent lipemia developed both in the rabbits receiving cholesterol and oil and in those which in addition were fed organic iodine, but the lipemia was more marked in the latter group.

The character of the lipemia differed from that observed in patients suffering from nephrosis in that the amounts of total, free and esterified cholesterol were proportionately more elevated than those of lipid nitrogen, lipid amino nitrogen (cephalin) or lipid phosphorus (phosphatides).

It is thought that in addition to lipemia and blood pressure a third factor influencing the receptivity of tissues to the deposition of fat is important in determining whether lipids will be deposited in the arterial walls. This factor may offer a partial explanation of the fact that atherosclerosis is a focal and not a general morbid change.

Case Reports

TUMORS OF ISLET TISSUE WITH HYPERINSULINISM IN A DOG

MAUD SLYE, B.A.
AND
H. GIDEON WELLS, M.D.
CHICAGO

Recently Slye, Holmes and Wells [1] published a study of the occurrence of tumors in the pancreas in the lower animals, which indicated that this site of primary malignant tumors is much less frequent in all other species of animals than in man. Among one hundred and twenty-five thousand mice in the Slye stock, approximately twenty thousand tumors have been found, only two of which arose in the pancreas. While the paper was in press we were fortunate in securing the body of a dog that had suffered from hypoglycemia, diagnosed clinically, supposedly on the basis of hyperinsulinism, in which multiple pancreatic tumors of the islet tissue were observed.

PROTOCOL FOR THE DOG

History.—A large, full-bred white pit bull-terrier, a female (never bred), died at the age of 12½ years. The dog was the property of one of us (M. S.) and therefore was under constant observation. She was in good health until 1932, when ulceration began in two of several cutaneous nodules, four of which were removed. Two of these nodules were removed under ether anesthesia, and later two more. One of the nodules presented the histologic structure of an early squamous cell carcinoma; two were benign epitheliomatous growths, and one was a simple cyst.

The dog seemed to recuperate from the ether unusually slowly but was apparently in good health, except for the tendency to become overfatigued easily, until Dec. 9, 1932, when an attack of marked weakness with lack of control of the muscles suddenly developed, so that she lay sprawled out, too weak to walk. On being given warm milk, which she took eagerly, she went to sleep and awoke apparently well. After this, she repeatedly had similar but less severe attacks, which were always relieved by food, generally beef or fish with some milk. On Jan. 1, 1933, another severe attack occurred, which lasted two hours and was relieved

From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

1. Slye, Maud; Holmes, H. F., and Wells, H. G.: Am. J. Cancer **23**:81, 1935.

by food. After this there occurred numerous similar but milder attacks, and as it was noted that feeding always gave relief the dog was thereafter fed four times a day and the activity was reduced. Because of the evident cardiac weakness, an electrocardiogram was made, which showed little evidence of abnormality.

In May the attacks subsided; in July 31, there was a very severe attack which lasted two hours and was relieved by food, but the next day such marked cardiac weakness was present that digitalis was given. After the severe attack of July 31, the attacks again subsided, perhaps because of the lower caloric requirements of warm weather, for with the return of cold weather the attacks reappeared with increased severity. During the attacks the dog seemed to be blind and ran into objects; she now began to have convulsions, there being three attacks in December 1933. At this time it was realized that the character of the attacks and especially the relief by feeding resembled the features of hyperinsulinism.[2]

An analysis of the blood was therefore made, and the sugar content was found to be but 30 mg. per hundred cubic centimeters and the calcium content normal. After this observation the feeding of plain milk chocolate was practiced whenever the slightest symptoms appeared, with resulting immediate and complete relief. From that time on the dog seemed to be perfectly normal as long as she received sugar occasionally. At first, it required a 10 cent bar of milk chocolate a day to keep the animal in condition, but later less and less was required, until finally only one or two small squares of such a bar were needed. Six days before death, for unknown reasons, she began to vomit and no longer retained any food.

It is to be mentioned that in 1931 a small, fatty subcutaneous tumor was noted, that several pea-sized cutaneous nodules developed and that five months before death a small, hard growth was found in the mammary gland which continued to grow slowly.

Autopsy.—Postmortem examination was made twenty hours after death (Dr. Mercy A. Southwick); the observations were, in brief, as follows:

The body of the dog weighed 37 pounds (16.8 Kg.), there being an abundance of fat. External examination disclosed the presence of several small tumors of the skin on the left foreleg and on the face. The largest, 1 cm. in diameter and 5 mm. thick, was on the left forefoot. On microscopic examination this tumor proved to be a sebaceous gland adenoma. There were five similar tumors on the face and many smaller ones on the body. The two right posterior mammary glands were enlarged, the more posterior being irregularly nodular and very hard. It measured 4 by 3.5 by 3 cm. and was not adherent to the skin. The other enlarged gland was 8 by 8 by 8 cm., and the enlargement was due to a mass of adipose tissue; the diagnosis was a simple benign lipoma. Another fatty tumor similar to the one already mentioned was noted 6 cm. anterior to the more anterior right mammary gland. No enlargement of the superficial lymph nodes was present.

Abdominal Cavity: A large amount of very pale, almost white, fat was present in the peritoneal cavity and in the omentum. The stomach was distended with fluid. In the colon at the splenic flexure there was an old kinking due to fibrous adhesions but no marked obstruction. The liver and spleen appeared normal and were free from tumor nodules. The left ovary was cystic and about 4 cm. in diameter. The right horn of the uterus contained a polyp, 1 by 0.5 cm.

Lungs: The lungs were atelectatic, and the cut surfaces appeared slightly wet and red. No tumor nodules were present here or in the mediastinal lymph nodes.

---

2. O'Leary, J. L., and Womack, N.: Arch. Path. **17**:291, 1934.

Trachea and Large Bronchi: The trachea and large bronchi appeared normal, except for the presence of gastric contents. The larynx was filled with a dark, almost black, semifluid material.

Thyroid: The thyroid was cystic and measured 6 by 4 by 4 cm., the cysts occupying all of the right lobe but an area 1.5 by 1.5 by 2 cm. The other lobe measured 6 by 4 by 4 cm. and was largely composed of reddish-yellow, necrotic-appearing tissue.

Gastro-Intestinal Tract: The stomach was about one-half full of semifluid, dark, foul-smelling material similar to that found in the larynx. Multiple superficial ulcers were present in the mucosa of the stomach, but postmortem changes were too advanced to permit determination as to whether or not the erosions occurred ante mortem.

Pancreas: The tail of the pancreas, throughout its length of 7 cm., was 5 mm. thick and 1.5 cm. wide and was firm. The head of the pancreas appeared to be infiltrated by fat, but occasional firm nodules were noted. The largest nodule measured 3 by 1.5 by 1 cm. Most of the other nodules were about 5 by 5 mm. One nodule near the head of the pancreas was 1 by 1 by 5 mm.; since it seemed well encapsulated and was surrounded only by fat, it may have been a lymph node. The pancreas appeared to be 18 cm. in length. So far as it was possible to determine, five firm nodules were present. Macroscopically, it was difficult to determine how much of the large nodule was composed of fibrous pancreatic tissue and how much was a nodule of firm, white, possibly tumor, tissue. When the second largest nodule was cut across, there was an area of reddish-black tissue occupying about one half of the mass; the rest of the nodule was firm and white and similar to the nodules already mentioned. One small nodule, measuring 5 by 3 by 5 mm., in the fatty peripancreatic tissue was determined to be a lymph node with secondary invasion of tumor tissue.

Histologic Examination.—Tumor of the Breast: The tissue was of mixed structure, consisting mostly of dense fibrous tissue in which were occasionally noted remnants of glands and many islands of bone containing a fibrous marrow. There were also occasional masses of cartilage and many areas of adenomatous character but no carcinomatous structures. The whole picture was that of the common mixed tumors of the mammary gland often noted in old dogs. The fatty subcutaneous tumor was a simple lipoma composed of mature fat cells.

Thyroid: The tissue consisted mostly of encapsulated adenomatous growths devoid of colloid and containing closely packed epithelial cells in which were many areas of necrosis, of hemorrhage and of fibrosis, such as are commonly seen in human adenomas of the thyroid. No invasion of the capsule or of the blood vessels was seen, and no mitotic figures were noted.

Uterus: The mucosa was thickened by a marked glandular hyperplasia, which accounts for the polypoid outgrowths observed on macroscopic examination.

Pancreas: All of the pancreatic nodules presented an adenomatous character but differed from one another chiefly in the proportion of fibrous tissue present. The epithelial elements, when not isolated by the fibrous overgrowth, tended to form solid masses of cells of uniform structure (fig. 1). These cells had round or slightly irregular nuclei, each of the nuclei being surrounded by a zone of cytoplasm, the width of which was about one half the diameter of the nucleus. The cells in general may be described as polyhedral. There was no tendency to form tubules. The appearance of the cells was in agreement with that of the cells of the islands of Langerhans; they did not resemble the pancreatic acinar cells. Some of the nodules contained much dense fibrous tissue, and others consisted mostly of epithelial elements. Unfortunately, postmortem degeneration had

removed most of the staining properties of the rest of the pancreas, so that it was impossible to report on the condition of the islets themselves or to study the granules of the tumor cells. The pancreas as a whole showed marked atrophy and replacement of the normal by adipose tissue and considerable fibrosis of the remaining portions of the gland. The general appearance suggested chronic fibrosis with atrophy and adenomatous hyperplasia of the islets. The character of the growth, as well as the absence of metastases in the lungs or in the cervical lymph nodes, excludes the possibility of these nodules being secondary growths from the adenoma of the thyroid. No remnants of acinar structure or of ducts were noted

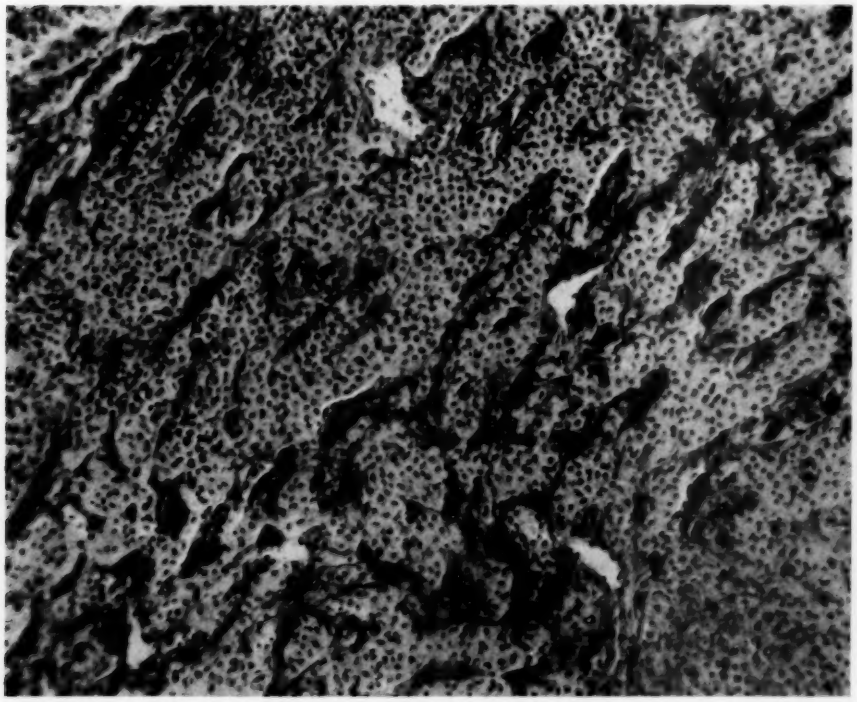

Fig. 1.—Adenoma of islet tissue. The section shows the similarity of the structure to that of islets and the separation of the cellular groups by an abundant stroma. The section is taken from one of the firm, apparently benign nodules. Van Gieson's stain; × 140.

in the tumor nodules. In places the tumor growth had a distinctly invasive character (fig. 2); in one part the fibrotic acinar tissue was definitely invaded by tumor cells. There were also places in which the adjacent peripancreatic tissues were infiltrated, and at one place a large nerve trunk exhibited invasion by tumor tissue. Invasion of perivascular lymphatics was also observed. A lymph node in the vicinity of the pylorus was also largely replaced by tumor tissue, which showed less fibrosis and a more characteristically malignant architecture than that observed elsewhere.

Kidneys: The basement membrane of the glomerules was slightly thickened, but no other marked changes were present in the kidneys, or in the spleen, the liver, the heart or the suprarenals.

Lungs: Sections from the lungs showed only bloody edema and atelectasis.

The character of the pancreatic growths, together with the definitely established hyperinsulinism, leaves no doubt that the nodules represented growths derived from the islands of Langerhans. The appearance of some of the nodules indicated that they were benign adenomatous growths, but at least two of the nodules showed characteristics of malig-

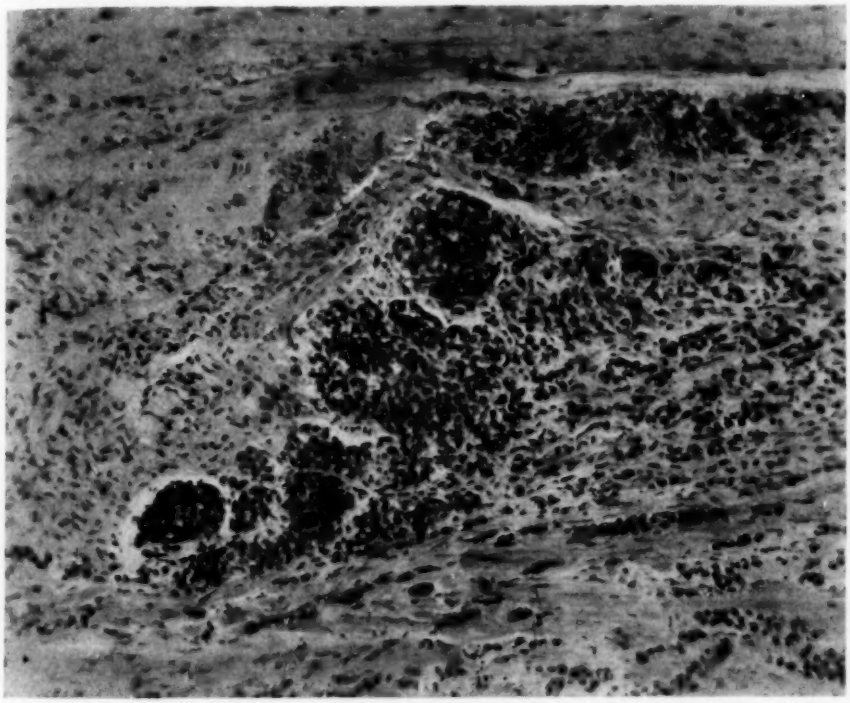

Fig. 2.—Adenoma of islet tissue. The section is taken from the invading border of a malignant nodule. Hematoxylin and eosin stain; × 140.

nant growth with definite invasive properties. One nodule was distinctly a lymph node largely replaced by tumor tissue. This case differs from the case of a malignant tumor of the islet tissue in a dog reported by Bru [3] in that hepatic and cardiac metastases were also present in his case. It is extremely unfortunate that postmortem changes were so advanced in our case that it was not possible to make adequate histologic study of the pancreas, to say nothing of determinations of insulin and glycogen.

3. Bru, P.: Rev. méd.-chir. d. mal. du foie **2**:40, 1927.

SUMMARY

Observations are reported on a dog which exhibited symptoms of hypoglycemia for about two years and in which the blood sugar was demonstrated to be low. The symptoms could be relieved immediately by the feeding of sugar and recurred in the absence of sugar. At autopsy there were observed nodules in the pancreas with the histologic appearance of tumors derived from the islet tissue. Some of the tumors seemed to be benign, but at least two appeared malignant, and an adjacent lymph node was almost completely replaced by tumor tissue. As is common in old dogs, multiple tumors were present, including a large benign mixed tumor of the mammary gland, two subcutaneous lipomas, multiple cutaneous tumors and an adenoma of the thyroid.

Laboratory Methods and Technical Notes

MODIFIED METHOD FOR STAINING GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS IN TISSUE SECTIONS

I. Rudnikoff, M.D., and Helen Stawsky, B.A., New York

The frequency with which one is called on to stain for gram-positive and gram-negative organisms in paraffin sections makes it desirable to have a rapid and efficient method for this purpose. Heretofore the only available procedure for the staining of gram-positive and gram-negative organisms in a single preparation has been the Brown and Brenn bacterial stain. However, the preparation of reagents for this technic is time-consuming, and extreme care is necessary in the various procedures for satisfactory results.

The Brown and Brenn [1] method for differential staining for gram-positive and gram-negative bacteria in tissue sections is as follows:

1. Stain in hematoxylin for from two to five minutes.
2. Decolorize in acid alcohol.
3. Dilute 1 cc. of stronger ammonia water in 100 cc. of water.
4. Wash with water.
5. In a small vial mix 5 drops of 5 per cent aqueous solution of sodium bicarbonate with 0.5 per cent phenol as a preservative—with about 0.75 cc. of 1 per cent (by weight) aqueous solution of gentian violet. Pour immediately on the slide and stain for two minutes.
6. Wash quickly in water.
7. Cover with compound solution of iodine for one minute.
8. Wash with water. Blot.
9. Decolorize in 1 part of ether plus 3 parts of acetone; drop this on the slide until no more color comes off. Blot.
10. Stain for five minutes with rosaniline hydrochloride (0.055 Gm. in 100 cc. of water) or basic fuchsin (0.1 cc. of a saturated aqueous solution in 100 cc. of water).
11. Wash in water. Blot but do not allow to dry.
12. Pass through acetone.
13. Decolorize and differentiate by dropping over the section a solution of 0.1 Gm. of trinitrophenol in 100 cc. of acetone until the section becomes yellowish pink. (This is the most critical stage of the process, and it should be carried out by holding the slide over a white plate or dish.) Most of the fuchsin should be decolorized from the tissue, but the gram-negative bacteria should remain red.

From the Department of Laboratories, Lebanon Hospital.

1. Brown, J. H., and Brenn, L.: Bull. Johns Hopkins Hosp. **48**:69, 1931.

14. Pass successively through acetone, acetone-xylene and xylene.
15. Mount in balsam.
16. The nuclei were stained brown; cytoplasm, yellowish; the gram-positive bacteria, deep violet or black, and the gram-negative bacteria, bright red.

The proposed modification of the Brown and Brenn method is as follows:

1. Deparaffinize the section in the routine manner.
2. Apply routine Gram stain as used on bacteriologic smears, i. e.:
   (*a*) Apply aniline-gentian violet for from five to ten seconds.
   (*b*) Treat with Gram's iodine for one-half minute.
   (*c*) Decolorize with 95 per cent alcohol until the section is colorless. Wash.
   (*d*) Counterstain with aqueous fuchsin or carbolfuchsin for from five to ten seconds.
   (*e*) Wash with water.
3. Blot almost to dryness. Pass through acetone.
4. Decolorize with 1 per cent trinitrophenol in acetone until the section appears yellow.
5. Pass through acetone, acetone-xylene and xylene. Mount in balsam.
6. The gram-positive bacteria were stained deep violet; the gram-negative bacteria, bright red; the nuclei, violet, and the cytoplasm, yellowish.

This method is rapid, consuming only from five to seven minutes. In various hands it has given accurate results with both gram-negative and gram-positive organisms.

General Review

THE HUMAN CORPUS LUTEUM

J. P. PRATT, M.D.
Surgeon-in-Charge, Division of Gynecology and Obstetrics, Henry Ford Hospital
DETROIT

(*Concluded from page 425*)

PATHOLOGY

Inflammation.—The frequency of oophoritis and other inflammatory conditions of the pelvis is well known. Included in the general inflammatory process, the corpus luteum may be involved to any degree, the lesion ranging from one of microscopic character to complete destruction by suppuration. However, a normal corpus luteum may be observed in close proximity to a lesion, or the corpus luteum may be an isolated site of infection. While the most frequent invading organism is the gonoccoccus, other relatively common invaders are the staphylococcus, the streptococcus and the colon bacillus. Tuberculosis is rarely found in this structure independent of its surroundings. A recent report by Kaijser [137] gives the details of a case of an adherent cyst of the left ovary, about the size of a child's head. The purulent contents yielded a pure culture of the paratyphoid bacillus. He found reports of three similar cases in the literature. Madelung is referred to by him as having collected forty-nine instances of typhoid infection.

Abscess of the corpus luteum has been frequently reported. One of the earliest of such reports is that by Négrier [22] in 1840, who wrote: "I do not doubt that the disease of the ovary would be anything else than suppuration of the yellow vesicle, the wall of which has been distended and torn following the accumulation of purulent material." He also believed that inflammation of a vesicle may terminate by resolution, induration or gangrene. Orthmann [138] reported twenty-one abscesses of corpora lutea out of a total of thirty ovarian abscesses.

The histologic structure of the wall of an abscess of a corpus luteum necessarily varies with the extent of the inflammatory involvement. However, Novak and TeLinde [139] described the wall of a typical abscess as "yellow in color, usually a shade paler than that of the lutein layer of the normal corpus luteum. Its inner surface is almost always folded

137. Kaijser, R.: Acta obst. et gynec. Scandinav. **14**:232, 1934.

138. Orthmann: Zentralbl. f. Gynäk. **21**:798, 1897; cited by Novak, E., and TeLinde, R. W.: Bull. Johns Hopkins Hosp. **34**:301, 1923.

139. Novak, E., and TeLinde, R. W.: Bull. Johns Hopkins Hosp. **34**:289, 1923.

and often quite wrinkled, presenting many alveolar markings somewhat similar to those of alligator skin, except that they are much finer meshed"; but, he wrote, "It should at this point be emphasized that many yellow-walled abscesses occur in the ovary which are not of corpus luteum origin." Degenerative products of the wall of any abscess may give rise to the yellow color, and Kehrer styled the large leukocyte-like cells as "pseudo-lutein cells."

The milder inflammations tend by hyperemia to increase the size of the individual lutein cells as well as that of the whole structure, which leads to an increase in function. The increased hyperemia also furnishes a basis for the frequency with which hemorrhages occur in the ovary. Likewise, the increased activity of the follicular apparatus is manifested clinically by the tendency to hypermenorrhea. Therefore, those who attribute the progestational hypertrophy of the endometrium to the influence of the corpus luteum would find in the stimulus of inflammation a cause for increased hypertrophy of the endometrium in such cases.

Many have speculated concerning the manner in which infection reaches the corpus luteum. While some contend that at the time of the rupture of the follicle an opening is present which may serve as a portal of entry for the infecting organism, no sound proof has been presented to substantiate this view. There are, on the contrary, strong reasons against this, for the opening is usually soon plugged, and before this occurs the fluid is flowing outward. A much more likely portal of entry is the lymphatic supply, for the lymphatics of the pelvis in general and of the ovaries in particular have been demonstrated to contain bacteria (Schröder). Sampson [140] favored the blood stream as a source of infection of ovarian cysts. He reported three cases of infected endometrial cyst of the ovary. The possibility of direct invasion is admitted. A recent report by de Grisogono [141] illustrates direct invasion of the corpus luteum from the appendix. It is evident that one cannot generalize on the source of infection; the source in the individual case must be considered. Probably each of the portals mentioned is at some time the site of infection.

Hematoma and Hemorrhage.—Ovarian hematomas and hemorrhages are popular subjects and have received extensive attention in the literature. Rollin [142] in 1889 believed all authors unanimous concerning the frequency of hemorrhages, and in his opinion no other organ in the body is so frequently the site of hemorrhages as the ovary. Novak [143]

140. Sampson, J. A.: Am. J. Obst. & Gynec. **18**:1, 1929.
141. de Grisogono, A.: Boll. d. Assoc. med. triest. **24**:270, 1933.
142. Rollin, F.: Des hémorrhagies de l'ovaire, Paris, G. Steinheil, 1889.
143. Novak, E.: Bull. Johns Hopkins Hosp. **28**:349, 1917.

in 1917 confirmed this opinion. However, some recent observations tend to show that some of the hemorrhages described are due to manipulation of the specimen during removal.

To distinguish hemorrhage from the corpus luteum from hemorrhages originating in other portions of the ovary is not always easy even today. It is far more difficult to evaluate properly the descriptions in the early literature, for by the written descriptions one cannot always be sure that the lesion originated in the ovary rather than in some other pelvic structure. Furthermore, pelvic hemorrhages were recognized before the corpus luteum was known. Then, too, after the corpus luteum was recognized as a source of bleeding, ectopic pregnancies were not satisfactorily separated from the other causes. Long after the corpus luteum was recognized as a source it was believed that ovulation occurred at the time of menstruation, so that many of the hemorrhages attributed to the follicle at the time of menstruation must, in reality, have been of corpus luteum origin.

The distinction between hemorrhage and hematoma is not always clear, for some authors class blood in the cavity of the follicle or corpus luteum as hemorrhage while others consider such lesions as hematomas. Others reserve the term "hematoma" for infiltration between the layers of tissue. In the earlier literature histologic data were lacking. Therefore, in the first part of this discussion no attempt will be made to distinguish hemorrhage from hematoma, but the general term "hemorrhage" will be used.

The first comprehensive review of the subject of pelvic hemorrhages was written by Voisin [144] in 1860 (retro-uterine hematocele), who collected fifty instances. In his illuminating review many of the ancient writings were carefully considered and were thought to contain descriptions of pelvic hematocele. A case report was quoted verbatim from Hippocrates, who was purported to have illustrated this condition. The reviewer divided his exposition into two parts, concerning which he wrote: "The first will comprise all the observations before 1850 which are scattered through diverse medical collections, and which have been published without their authors knowing the condition with which they were dealing. The second will begin with 1850, a time at which Professor Nélaton gave to retro-uterine hematocele, which he has thus named, so exact a place in nosology." It seems to be the general opinion of contemporary authors that Nélaton was responsible for considering the condition of retro-uterine hematocele as an entity, and that in some cases the hemorrhage originated in the ovary. His teaching stimulated great

144. Voisin, A. F.: De l'hématocèle rétroutérin, Paris, J.-B. Baillière & fils, 1858.

interest in the subject. However, in 1933 Cornil and his co-workers [145] maintained that the first case was reported by Ruysch in 1737, but Voisin [144] quoted Ruysch to show that he described a hemorrhage from the tube and not from the ovary. Voisin credited Richet in 1854 with being the first to explain retro-uterine hematocele by rupture of varicosities of ovarian veins. Likewise, he credited Scanzoni in 1858 with being the first to teach that hemorrhage from the tube might be a cause. But Cornil [145] wrote that Denuce in 1853 formulated the hypothesis of retro-uterine hematocele originating from extra-uterine pregnancy.

The excellent critical review by Voisin [144] is well worth reading in full, as it reflects the opinions current at that time. In accord with the prevailing idea that a graafian vesicle ruptures at the time of menstruation, he explained many of the hemorrhages by a spontaneous rupture of the follicle, but in the light of present knowledge he was in reality dealing with bleeding from a corpus luteum, since it is now known that the follicle rarely, if ever, ruptures at the time of menstruation. He indicated predisposing causes, such as systemic diseases, local diseases of the ovary and many conditions leading to hyperemia. It is interesting to note his comment that in treatment puncture of the hematocele should be undertaken with caution on account of the dire effects of infection. This attitude is easily understood, since at that time aseptic surgery was not yet in vogue. In the hands of physicians of that day, conservative expectant treatment produced much more favorable results. The symptoms noted by Voisin may be summarized as those due to hemorrhage within the body and irritation of the peritoneum.

Cornil and his collaborators [145] cited a long list of contributions to the subject of ovarian hemorrhage, but the list is by no means complete. According to him, Fordyce in 1888 was the first to observe follicular hemorrhage. Eberhardt in the same year was the first to report hemorrhagic oophoritis. Pilliet [146] in 1893, according to Cornil, was the first to attribute hemorrhage to the corpus luteum. However, Pilliet referred in his communication to Robin as having noted such a hemorrhage in 1856.

Rollin [142] in 1889 collected reports of fifty-two cases of hemorrhage from the ovary, with autopsy, found in the French and other literature. Many of these cases had already been cited. Regarding the fine line of distinction to be drawn between the physiologic and pathologic, he wrote: "Formerly it was believed that at the time of rupture of the vesicle for setting free the ovum an intra-vesicular hemorrhage was produced and that the clot thereby formed was the origin of the yellow

145. Cornil, L.; Mosinger, M., and Picaud: Gynéc. et obst. **27**:491, 1933.
146. Pilliet, A. H.: Ann. de gynéc. et d'obst. **40**:366, 1893.

body. Today one tends to attach little significance to this hemorrhage." This old idea of the corpus luteum being formed from the clot was definitely abandoned, and hemorrhage was thought to be merely accidental in the evolution of the corpus luteum.

Rollin frankly stated that hemorrhage of the corpus luteum does not appear to have any great surgical importance. This statement, however, is not supported by his reports of cases. His error of interpretation was due to the view prevailing then that ovulation occurs at the time of menstruation, and many of the hemorrhages described in his reports are specifically stated to have occurred at menstruation. Further analysis would probably eliminate some of his so-called cases of hemorrhage and place them in the category of examples of endometriosis, for there are described cavities containing dark or pitch-black tarry material, the enclosing wall being thick and adherent to the surrounding structures.

In the interval between the report of Voisin in 1869 and that of Rollin in 1889 the general improvement in surgical technic influenced favorably the treatment of pelvic hemorrhage. Early operation came to be the treatment of choice. Since the time of Voisin and Rollin the medical profession has not lacked interest in hemorrhage in the pelvis, as indicated by Cornil's [145] citation of a long list of contributions extending to 1933. Von Beust [147] in 1914 reemphasized the ovarian source of hemorrhage. He collected a group of case reports from the literature, which he critically reviewed. He grouped the cases as: (1) those of nonperforating hemorrhage, (2) those of free intra-abdominal hemorrhage and (3) those of encapsulated intra-abdominal hemorrhage—hematocele. Most of the material was obtained at operation, the specimens removed being subsequently examined histologically. Many of these hemorrhages were unquestionably of corpus luteum origin; others came from follicular cysts, while some undoubtedly represented endometriosis. Since his symptomatology and differential diagnosis are applied generally to the whole group of pelvic hemorrhages, they are not useful in defining the characteristics of hemorrhage from the corpus luteum. However, the influence of his work is still felt in focusing attention on the ovary as a source of hemorrhages to be considered carefully in differential diagnosis. Furthermore, his reports demonstrate the importance of early operation in suspected cases.

Since von Beust's report, other cases have been added from time to time. Thus, Johnson [148] in 1930 collected a total of seventy-seven

147. von Beust, A. T.: Lebensbedrohliche intraabdominelle Blutungen aus geplatzten Folliculär- und Luteincysten des Ovariums, Zurich, Gebr. Leemann & Co., 1914.

148. Johnson, V. E.: Am. J. Surg. **9**:538, 1930.

instances, and Meigs and Hoyt added twenty-five more, so that now there are more than one hundred on record. The details recorded are not adequate to permit correct allocation to the corpus luteum. The symptoms produced by hemorrhage in the pelvis are practically the same regardless of whether or not the corpus luteum is the source. The main guiding factor in fixing the source of hemorrhage is the time relation of the onset of symptoms to the phase of the menstrual cycle.

There are two types of ovarian hemorrhage: the mild and the fulminating. Most of the references in the literature are to the latter, more easily recognized type, for the symptoms of mild hemorrhage are so inconspicuous that they are frequently overlooked. However, many of the earlier writers cited mentioned finding accidentally in specimens examined small hemorrhages to which no symptoms had been related. Priestley [56] in 1872 regretted that no accurate records concerning the condition and progress of the graafian vesicles during menstrual intervals were available. He described cases of pain in the ovaries during the midmenstrual period. Although ovulation and menstruation were thought to coincide, he wondered if preparation in the ovary for its next menstruation might not commence from ten to fourteen days before menstruation and initiate a recurrence of vascular excitement. This was reemphasized by Storer [149] in 1900, who illustrated the condition by several cases of his own, as well as by others cited from the literature. Other writers have mentioned the condition so inconspicuously that little attention has been paid to it until recently. Brakeley and Farr [150] in 1926 reported two instances in which the diagnosis of ovarian hemorrhage was made, although no operation was performed, and they concluded that with rare exceptions operative treatment is not indicated. Of the twenty-five cases in which operation was resorted to by Meigs and Hoyt,[151] only two were of hemorrhage of the fulminating type. They demonstrated that the diagnosis can be made before operation. There are many, however, who still doubt this.

In a recent paper I pointed out that differential diagnosis of hemorrhage from the follicular apparatus might well include the symptomatology of ectopic pregnancy, endometriosis, twisted ovarian pedicle and gastro-intestinal disturbances, especially appendicitis. Ectopic pregnancy and twisted ovarian pedicle are more likely to be confused with fulminating than with mild ovarian hemorrhages, so that in either instance operative treatment would be necessary. The pain and tenderness of endometriosis are usually more intense near the time of menstruation and subside during the intermenstrual period. Furthermore,

149. Storer, M.: Boston M. & S. J. **142**:397, 1900.
150. Brakeley, E., and Farr, C. E.: Am. J. M. Sc. **172**:580, 1926.
151. Meigs, J. V., and Hoyt, W. F.: Am. J. Obst. & Gynec. **25**:532, 1933.

they more frequently occur later in the reproductive cycle than the mild hemorrhages. From a practical point of view, therefore, the main problem for differential diagnosis is the distinction between appendicitis and the mild type, because the more serious condition of ectopic pregnancy is to be differentiated only from the more severe hemorrhages. In appendicitis the symptoms are progressive while in mild hemorrhage the symptoms are slight and do not progress to any great extent. Therefore, it is safe to wait before operation long enough to establish the trend of symptoms. This has now been done successfully many times. A carefully taken history of the onset of symptoms and attention to the localization of the pain and tenderness are extremely important.

It is generally accepted that the site of election is preponderantly in the follicular apparatus, which may be accounted for by frequent physiologic and pathologic hyperemias. However, much confusion exists regarding the nature and origin of these hemorrhages, concerning which Shaw [152] wrote: "Until recently deplorable errors were made, the majority due to ignorance of normal ovarian histology and physiology." He ascribed the hematomas of the follicle and the corpus luteum to the same cause, namely, rupture of the newly formed capillaries, the walls of which are delicate and easily ruptured under the influence of hyperemia. In the follicle these capillaries are only in the thecal layer, but in the corpus luteum they have grown into and through the membrana granulosa. In the first instance the hematoma appears as an extravasation in the theca, while in the latter it may reach the cavity of the corpus luteum. Further, in regard to the localization, Novak ranked the atretic follicle first, but Shaw frankly disagreed with Novak, and likewise he considered the stromal hematoma of Pfannenstiel extremely rare. Shaw considered the ripening follicle the most frequent site.

A true evaluation of the normal ovary is difficult to attain, for the literature concerning the normal ovary is inadequate for obvious reasons. The best material is obtained at operation, and naturally most operations are performed on account of preexisting pathologic states. My observation is that a normal ovary does not frequently show evidence of hemorrhage, but that even the gentlest manipulations exerted to bring the organ into clear view readily produce slight hemorrhages, a fact which is easily explained when the delicacy of the newly forming capillaries is considered. The traumatization during removal accounts for many of the recent hemorrhages seen in laboratory specimens. This risk of traumatic hemorrhage is increased when hyperemia exists from any cause. The frequency of the occurrence of

152. Shaw, W.: J. Obst. & Gynaec. Brit. Emp. **34**:469, 1927.

hemorrhage will be greatly limited if the trauma of examination before and during an operation is excluded, for the ovary naturally occupies a protected position.

The mechanism of bleeding varies somewhat according to the time in the menstrual cycle at which the accident occurs. From an analysis of the cases which have been reported, there appears to be a grouping of the onsets of bleeding around the time of ovulation and just preceding menstruation. Concerning the mechanism of bleeding at the time of ovulation, Schröder maintained that there are only two possibilities: (1) bleeding from the veins in the neighborhood of the point of rupture, these vessels having been torn at the time of rupture; (2) a decided increase in the capillary bleeding as it occurs normally at the time of the rupture of the follicle from the theca interna, or bleeding from a varix formation in the region of the theca interna. The entire interior of the follicle is then quickly filled with blood, the membrana granulosa is usually destroyed, and the bleeding overflows from the point of rupture into the abdominal cavity.

Regarding bleeding into the corpus luteum, Schröder maintained that 70 per cent of all corpora lutea show some evidence of hemorrhage about the time of menstruation. The source of the bleeding is the newly arisen capillary area inside of the membrana granulosa. As a rule, the bleeding is so slight that there is little or no dilation of the corpus luteum. With more extensive bleeding, the covering of the ovarian tissue may give way and the blood escape into the peritoneal cavity, or if the covering remains intact a hemorrhagic cyst is formed which may be as large as a child's or an adult's head. Such hemorrhagic cysts are especially prone to infection because the content is an ideal culture medium and there is insufficient protection against invasion by bacteria on account of the lack of blood supply. Novak [143] emphasized the delicacy of the capillaries during the stage of vascularization and believed hemorrhages at this stage to be very frequent. Hemorrhages found during maturity and retrogression are probably old, having really occurred during the stage of vascularization.

From what has been said it is evident that some bleeding in the follicle and corpus luteum is physiologic. The transition from the physiologic to the pathologic is often difficult to determine. The degree of the symptoms in pathologic conditions is in proportion to the rapidity and the extent of the bleeding.

The intensive study devoted to hemorrhages and their consequences has produced a gradual evolution from a confused grouping of all cases of ovarian bleeding together to a separation according to the various parts of the ovary involved and a correlation with the phases of the menstrual cycle, and from recognition only at autopsy to correct

preoperative diagnosis in some instances, and from expectant treatment to active surgical intervention. Viewing this problem as a whole, one feels that satisfactory progress has been made and an adequate foundation laid for future development and better understanding of the problem.

Expulsion, Prolapse or Shedding of the Corpus Luteum.—Projection of the corpus luteum above the surface of the ovary is commonly observed. The amount of projection varies considerably, and at times the corpus spreads out over the surface of the ovary like a mushroom. The process may extend even farther until the corpus is expelled from the ovary and drops into the culdesac. Such a process has been variously styled "prolapse," "expulsion and shedding" or "extrusion of the corpus luteum." Schröder [61] quoted Suppow as having in 1912 observed five such cases. Stolper [153] in 1922 reported a case in which, on operation for ectopic pregnancy, a cherry-sized structure was found in the pouch of Douglas, which proved to be a corpus luteum. He cited Halban as believing that a corpus luteum lying free can still function. Conclusions concerning the preservation of function of a prolapsed corpus luteum can be only speculative, for there are no reports in the literature which cite the observation of a prolapsed corpus without its removal. Therefore, there are no data from which to determine the effect of a corpus lying free in the pelvic cavity.

On the basis of an analysis of special observations on the subject, Kanevsky [154] concluded that inflammatory and cystic changes in the ovarian tissue exert an influence on the corpus luteum and cause nutritional disturbance with inflammatory and cystic changes which favor the onset of its prolapse. According to him, the separation may occur not only in the lutein layer but also in the theca in case its nutrition is disturbed and the necrotic and necrobiotic processes continue.

Prolapse has undoubtedly been frequently observed but has not been considered of sufficient practical importance to merit a report.

Cysts.—Definition of corpus luteum cyst is difficult since, as already shown, many corpora lutea are normally distended with fluid. Even though an anatomic standard is determined, a corpus luteum which appears cystic may, nevertheless, be functionally active. According to the inclusiveness of the definition, statements concerning frequency of occurrence vary. Thus Santi considered all cystic corpora lutea abnormal, while Martin spoke of cysts only when the structures reached a size larger than the ovary. Novak and TeLinde [139] in 1923 considered that normal cystic corpora lutea are rarely more than 2 cm.

153. Stolper: Klin. Wchnschr. **1**:922, 1922.

154. Kanevsky, E. I.: Vrach. delo **14**:779, 1931.

in diameter, and suggested that this size be arbitrarily selected as the line of demarcation.

According to Novak and TeLinde,[139] the first corpus luteum cyst to be reported was described by von Rokitanski in 1859. However, Robin [12] in 1856 described a hemorrhage into a follicle at the time of menstruation which produced a cyst that projected above the surface of the ovary, the projection attaining the size of a walnut. Considering the time in the menstrual cycle, one concludes that he probably dealt with a hemorrhagic cyst of the corpus luteum. Other authors in the next three decades described hemorrhages, free and encapsulated, occurring at the time of menstruation, therefore probably originating in the corpus luteum, but none of these were particularly informative, on account of inadequate histologic data and confusion concerning the time of origin of the corpus luteum.

The first important contribution to the subject was made by Fraenkel [155] in 1898, when he described six corpora lutea varying in size from that of a hazelnut to that of a peach. As a result of his histologic study he divided such corpora into classes according to the lining of the cyst: (1) lined with lutein cells only; (2) lined with fibrous tissue within the lutein layer; (3) lined with endothelium-like cells. For the most part this classification was followed until Novak and TeLinde [139] in 1923 pointed out that the variation in appearance was undoubtedly due to the different age phases of the same process. Their study of nineteen corpus luteum cysts led them to classify such cysts into recent and old cysts.

The lesions in the pelvis with which corpus luteum cyst has been associated as recorded by most authors are similar. The following tabulation given by Schröder [61] expresses the situation as a whole:

	Times
(*a*) With chronic inflammatory disease of the adnexa uteri	34
(*b*) With tubal abortion	10
(*c*) With myoma	4
(*d*) With a movable retroflexed uterus	1
(*e*) With ovarian tumors (dermoid cyst, adenoma and carcinoma)	4
(*f*) With carcinoma of the cervix	1
(*g*) With intra-uterine pregnancy	2
(*h*) With otherwise normal findings	2

The cysts are seldom large. Novak's largest one measured 4 cm. Schröder compares the larger ones to a large goose egg. There are descriptions of corpus luteum cysts that reached the size of a head. However, in these instances, the histologic data are inadequate to insure an accurate diagnosis.

The wall of the corpus luteum cyst shows little or no waving, the pressure from within having flattened the folds ordinarily seen in a normal corpus. In general, the fluid is limited by an endothelial layer

155. Fraenkel, L.: Arch. f. Gynäk. **56**:355, 1898.

underneath which is a lutein layer, sometimes incomplete or broken, especially in the larger cysts. In the size of the lutein cells, their lipoid content, the extent and amount of vascularization, the penetration with tender fibrils, the outer thecal layer and the characteristic fibrous changes in regression, the cystic corpus luteum corresponds in every way with the normal corpus. It is possible, therefore, to read in a corpus luteum cyst the exact age from the structure of the wall. Combining the clinical and anatomic findings, one concludes that cystic formation of a corpus luteum is secondary, and that such a corpus differs in no important manner, except in size, from an ordinary corpus luteum. Every transformation from the normal corpus luteum has been observed. Cystic corpora lutea as well as corpus luteum cysts have been found at all times in the cycle but are more frequent in the latter half of the intermenstrual period. For this reason a separate classification of cystic corpora lutea is not necessary.

Some have assumed that the cysts cause hyperemia and frequently adhesions, but more probably, as others contend, the adhesions are a factor in the formation of the cysts.

The content of the cysts is usually gelatinous. In the larger cysts it may be watery, clear or sometimes straw-colored; not infrequently the fluid is blood-stained.

The tissue of the ovary surrounding the corpus luteum cyst, although varied, does not differ materially from that which one is accustomed to observe surrounding a normal corpus luteum.

In association with the age changes in the corpus luteum cysts, corresponding transformations are found in the endometrium, provided there are no complicating lesions.

There are no characteristic symptoms of corpus luteum cysts in ovaries otherwise normal. When tubal pregnancy, intra-uterine pregnancy, abortion or inflammation coexists, irregularity in bleeding is to be expected. A large majority of the cysts occur in association with inflammatory conditions and, as mentioned under the subject of inflammation, there is usually an increased flow. Frequently such cysts have been observed to disappear spontaneously. Pain and tenderness in the presence of a corpus luteum cyst are more likely to be due to the associated conditions, particularly to inflammatory processes. According to Schröder,[61] von Oettingen, Matthes and Fraenkel attributed to the corpus luteum cyst a causal relation to protracted parametritis, chronic induration, deformities, sterility and amenorrhea. Keller reported the frequency of corpus luteum cyst in tubal pregnancy.

Corpus luteum persistens is a condition long known to veterinarians, occurring in association with sterility in cattle. They were at first inclined to regard this as having an inhibitory influence on ovulation,

but now they attribute the persistence of the corpus luteum and the associated sterility to missed abortion. Schröder [61] considered the persistent corpus luteum cyst to be plausibly and satisfactorily explained by missed abortion. At any rate, manual rupture of the persistent corpus luteum cyst reestablishes the normal cycle and fertility in cattle. The identity of corpus luteum persistens of cattle with that of the human being first assumed by Halban [156] was questioned by Novak and TeLinde [139] and others. Novak and TeLinde maintained that it is necessary to know more about the function of a normal corpus luteum before attempting to explain corpus luteum persistens and its relation to sterility in cattle. They further stated that there is much reason to believe that the ovum is the dominant factor in the physiology of menstruation, and that theoretically, at least, one of the possible manifestations of ovular abnormality is the so-called corpus luteum persistence. According to Novak and TeLinde, therefore, corpus luteum persistens depends on the primacy of the ovum, a doctrine championed by Meyer. But it seems doubtful that the unfertilized ovum has an important influence on the life history of a corpus luteum or a corpus luteum cyst. (This is discussed in the section on function.)

Complications of corpus luteum cysts are: inflammations, hemorrhages and rupture. The inflammations have already been discussed in the previous section, and reference has been made to the hemorrhages. The hemorrhagic cyst described by Boeckel [157] in 1861 may be mentioned here. This was a large cyst palpated through the abdominal wall. Boeckel treated the cyst by puncture and irrigation of the cavity with iodine. The content of the cyst was described as typical of the now better known chocolate cysts. Even his report of the autopsy in the case is not sufficient to allow one to determine whether or not the origin was from a corpus luteum, but such a source is at least suggested by his description.

The rupture of a corpus luteum cyst has been observed following examination just preceding operation. It has also been assumed to occur in instances in which operation has not followed. The symptoms observed are those of irritation of the peritoneum and are not serious unless the hemorrhage is excessive.

Sampson [140] in 1929 observed in a group of ovarian hemorrhagic cysts that a portion of the hematoma, usually the deeper layers, was lined by luteal membrane, the exact origin of which, in some specimens, was difficult to determine; the rest of the cyst, usually toward the perforation, was apparently relined by invading epithelium. With the advance of the epithelium the luteal membrane retrogressed. The question of

156. Halban, J.: Zentralbl.f. Gynäk. **39**:409, 1915.
157. Boeckel, E.: Gaz. méd. de Strasbourg **21**:79, 1861.

the origin of chocolate cysts of the ovary containing luteal tissue is still unsettled. Further discussion of this would require reiteration of the various theories propounded to explain the origin of endometriosis.

Shaw described an interesting case of bilateral lutein cysts complicating uterine fibromyoma which probably belongs in the same category as those described by Sampson.[140] He found several cysts in each ovary, some of which were pseudomucinous. Others were partly lined by lutein cells and contained tarry fluid. However, the majority of the cysts did not contain tarry fluid, and the tumors were not surrounded by peritoneal adhesions. He called attention to the frequency with which lutein cells are found in tarry cysts in general. In some of the cysts he found lutein cells with no tarry fluid, but considered that this was an exception to the rule. According to his opinion, knowledge of the etiology of ovarian cysts is primitive, and the theories that have been advanced up to the present are unsatisfactory. The frequency with which ovarian tumors are bilateral suggested to him that some stimulus is exerted by way of the blood stream, and if there is a suitable nidus in the ovary, formation of a tumor follows. He further suggested that in the case of tarry lutein cyst of the ovary the nidus in the ovary is heterotopic epithelium of the type found in the wall of the cyst. His observation of multiple cysts of such a varied type in both ovaries is unique.

A condition sometimes confused with corpus luteum cyst should be mentioned in passing, namely, multiple lutein cysts of the ovary frequently described as occurring with hydatid mole or chorioma. The finding of the cyst in association with these abnormalities of the uterus is not constant, the frequency reported by different authors varying widely. It has also been a debatable question whether the condition in the uterus caused the cyst or the cyst the abnormalities in the uterus. At any rate, it is now generally accepted that the lutein cells lining these cysts are of the type of the theca interna and are therefore related to atretic follicles and not to corpora lutea.

Hyperplasia of the endometrium, a popular subject today, has been variously related to the condition of the corpus luteum. Thus, Curtis [158] found a persistent corpus luteum associated with hypertrophy of the endometrium and considered the cyst functionally responsible for this. The whole subject of endometrial hyperplasia has recently been reviewed by Burch and his associates,[159] who stated that as a general rule the presence of corpora lutea with hyperplasia of the endometrium is the exception. They expressed the belief that the occasional coincidence of corpora can probably be explained either by diag-

158. Curtis, A. H.: Surg., Gynec. & Obst. **35**:830, 1922.

159. Burch, J. C.; Phelps, D., and Wolfe, J. M.: Arch. Path. **17**:799, 1934.

nostic errors or by a nonfunctioning state of the corpora or by spontaneous or induced ovulation in the course of a disease. It is necessary here only to invite attention to the fact that absence of function of the corpus luteum has been noted in association with hyperplasia of the endometrium.

Tumors.—Classification of all or part of the ovarian tumors is complicated, difficult and unsatisfactory. Overlapping of terms is so frequent that it is often impossible to determine from the name of a tumor reported either its structure or its histogenesis. Although some tumors have been shown to contain lutein or lutein-like cells, it has been questioned on good ground whether any ovarian tumor is truly related to the corpus luteum. There are three tumors, however, which merit some consideration at this point: the so-called hypernephroma, the granulosa cell tumor and the luteoma. An increasing interest is attached to these tumors, at first on account of their structure but more recently on account of their function.

Meyer [160] said:

> It may appear unusual to state that tumors may possess function. Admittedly, however, every body cell functions even if abnormal; and cells of a new growth may exhibit a specific functional capacity exactly corresponding to the function of the tissue from which they arise. We know that the ovary plays a special rôle in the determination of sex characteristics both in the body as a whole and in the genital organs, therefore, it cannot be surprising to find that in some ovarian neoplasms the tumor cells functionate and participate in this process of development of secondary sex characters.

Clinical evidence of the functional influence of ovarian tumors has been frequently recorded with disappearance of function following the removal of the tumor. A striking example of this is the uterine bleeding associated with a granulosa cell tumor of the ovary occurring in a woman long after the menopause.

Fourteen hypernephromas of the ovary reported in the literature were critically reviewed by Glynn,[161] who concluded that only one true hypernephroma of the female pelvis had been recorded, a tumor arising in the broad ligament. This conclusion is in accord with the present trend to reclassify many of the tumors previously listed as hypernephromas. Wide variation in the histologic structure of primary neoplasms of the suprarenal cortex has led to great confusion in the nomenclature of these tumors.

In reviewing descriptions by nine different observers of solid yellow ovarian tumors, usually containing hemorrhagic and necrotic areas and sometimes a few degeneration cysts, Glynn stated that they were called

160. Meyer, R.: Am. J. Obst. & Gynec. **22**:697, 1931.
161. Glynn, E.: J. Obst. & Gynaec. Brit. Emp. **28**:23, 1921.

hypernephromas not only on account of their yellow color and perhaps the presence of fat, glycogen or lumens, but particularly on account of the general resemblance of the groups of clear or vacuolated cells lying in a capillary stroma to the zona fasciculata of the suprarenal cortex when loaded with fat. Further evidence of suprarenal origin was based on the general macroscopic and microscopic resemblance to the so-called renal hypernephroma.

Glynn reviewed microscopic sections of the tumors reported and reproduced thirty photomicrographs of these sections, which show great variation in structure. He believed that not any of the growths so described were truly hypernephromas, for the following reasons:

1. Embryologic Observations: While suprarenal cortical tissue is frequently found in the broad ligament, there is no proved case of its presence in the ovary. Sixteen observers reported thirty-four instances of suprarenal tissue in the broad ligament but only once was it close to the ovary.

2. Histologic Observations: The primary suprarenal hypernephroma is characterized by great variation in the shape and size of its cells and their nuclei, by absence of characteristic clear or very vacuolated cytoplasm and apparently by complete absence of well formed glandlike lumens. The so-called ovarian hypernephromas reviewed by him, while not resembling the primary tumors of the suprarenal glands, did bear a resemblance, more or less close, to the normal suprarenal cortex while, according to him, the resemblance of the suprarenal hypernephroma to the cortex is usually so slight that none but an expert would suspect its origin.

3. Clinical Observations: Suprarenal virilism was absent in the nine patients with lutein tumors who had not yet passed the menopause, while a hypernephroma arising in the broad ligament, where accessory suprarenal glands are common, does produce characteristic changes of sex characters.

Novak and TeLinde [139] were not convinced by the evidence for the lutein origin of all of the fourteen instances collected by Glynn. They particularly mentioned the case of Schaller and Pforringer reported in 1899 as being more probably an example of multiple thecal lutein cysts of the ovary associated with hydatid mole, for in this case such a mole was expelled from the uterus twelve days after the operation. They further objected to the inclusion of Grouzdew's case reported in 1903, for his tumor recurred in the lymphatic glands and on the peritoneum as a spindle-cell sarcoma.

Recent interest in the granulosa cell tumors and luteomas with particular reference to their functional capability seems to cast further doubt on the likelihood of hypernephroma occurring frequently, or at all, in the ovary.

The granulosa cell tumors of the ovary deserve slight consideration here merely because in some of these tumors lutein cells have been noted. These tumors cannot be looked on as true outgrowths of the corpus luteum or as a growth very closely simulating the corpus luteum.

for the lutein cells are probably of thecal origin. If one accepts Meyer's opinion of the histogenesis of the granulosa cell tumors, they can scarcely be considered in any way related to the follicular apparatus.

Meyer, who made an extensive study of these tumors, thought that they arose from undifferentiated cell rests and not from the epithelial cells of the true follicle. He[160] wrote: "It has never been demonstrated that such a growth could originate from the follicle, and it is more than unlikely that the granulosa cells of a true follicle could produce such a growth." Because he found most of these tumors in older women whose ovaries should no longer have contained follicles, he believed that it was necessary to look for some other cause than the follicle, because granulosa cells which do not participate in the normal development and normal function of the ovarian tissue remain uninfluenced by the menopause. The frequency of the occurrence of cell rests in the medullary portion of the ovary in the fetus, in young girls and in mature women and even old women past the menopause was evidence for him that they might be able to produce granulosa cell tumors under certain conditions, still unknown, at any stage in the life of the patient.

According to Novak and Long,[162] the granulosa cell tumors are now accepted as arising only from the early oophorogenic structure in the ovary.

The feminizing tendency of the granulosa cell group is taken as evidence that the constituent cells of the tumors produce follicular hormone. Neumann[163] in 1933, reviewing the granulosa cell tumors as producers of hormone, cited experiments in tissue transplantation as well as the results of examination of the blood and urine of patients bearing these tumors. Sufficient research has been devoted to the functional activity of these cells in recent years to prove conclusively that they are capable of producing the follicular hormone, but Novak theoretically assumes further that certain clinical manifestations indicate that they also produced corpus luteum hormone.

An excellent recent review of the granulosa cell tumors of the ovaries with a study of thirty-six cases of their own is that of Novak and Brawner. The similarity of the constituent cells of the granulosa cell tumor to the normal follicular epithelium at once suggests that the origin of the tumor is to be sought in some phase of follicular development. However, the view that such a neoplasm may arise from the adult follicle has been virtually abandoned. The argument against the tumor's arising from adult follicle cells, as given by Meyer, is that the follicular epithelium is a satellite tissue of short life, and that this life

162. Novak, E., and Long, J. H.: J. A. M. A. **101**:1057, 1933.
163. Neumann, H. O.: Endokrinologie **12**:166, 1933.

is dependent on the life of the ovum. It is difficult to believe that such transient, involuting tissue could give rise to neoplasms. Furthermore, the fact that so many tumors arise in women who are past the period of follicular activity is against such a theory. Circumstantial evidence for the origin from cell rests is the fact that the granulosa cell tumors are found in close relation to such cell rests.

Novak and Brawner [164] expressed the belief that the term "granulosa cell carcinoma" can be properly extended to include cases in which lutein-like transformations of some or all of the cells have occurred, that is, the folliculoma of Lecene and possibly the luteoma. They called attention to one case in which the tumor showed large amounts of lipoid substance. They asserted that the tumor had produced both follicular hormone and corpus luteum hormone, based on the microscopic appearance of the endometrium. Although lutein-like cells have been reported in various tumors, their origin and character have not yet been clearly defined. In general, they seem to be more like the thecal lutein cells than the granulosa lutein cells. The demonstration of a true granulosa lutein cell in ovarian neoplasms may rightly be questioned. Novak and Brawner state:

> To pursue this subject just a bit further, one may naturally inquire whether we may not consider the so-called luteomas, made up entirely of what are apparently lutein cells, as merely a finished stage of this lutein transformation of primarily granulosal tumors. This is particularly true because it is hard to believe that lutein cells, any more than adult granulosal cells, would give rise to neoplasms. Our knowledge of the real nature of luteomas is too meager to justify any statement as to their exact relation to the granulosal cell group, especially when we bear in mind the confusion existing in the literature because of the difficulty of distinguishing luteoma from adrenal tumors of the ovary (hypernephroma).

For the present, at least, it seems that luteomas might be reclassified and distributed between the group of granulosa cell tumors and that of aberrations from normal corpora lutea. The latter group would include the corpus luteum cysts and thecal lutein cysts. The criticism is valid that granulosa cells are transient, are rapidly undergoing involution through lutein cells and, therefore, having passed the acme of development, are not likely to give rise to neoplasms.

The demonstration that cells of ovarian tumors possess function has opened a new fertile field, exploration of which may reasonably be expected to clarify the whole subject of ovarian tumors.

At present a separate classification of luteomas is not fully justified. Therefore, a further discussion of these interesting ovarian tumors is not pertinent to the subject—the corpus luteum.

---

164. Novak, E., and Brawner, J. N., Jr.: Am. J. Obst. & Gynec. **28**:637, 1934.

COMMENT

The literature on the corpus luteum is voluminous. Often no distinction is made to indicate the species studied. It is difficult, therefore, to separate references to human beings from inferences from animals. In many instances no distinction is made between estrus and menstruation. For the most part, however, experimentation on animals has laid the foundation for interpretation of human problems. Errors arising from deductions have sooner or later been eliminated. Quite general agreement as to the anatomic structure of the corpus luteum has been attained, but the concept of its function is still in transition.

The advances made have been possible on account of the accumulated knowledge which has preceded. Recent progress in chemistry, epitomized by the isolation of theelin in pure crystal form from many sources including the corpus luteum, and the isolation of pure crystals of progestin from the corpora lutea of some animals, marks the beginning of a new era. The discovery of the control of ovarian function by the anterior lobe of the hypophysis is important. It is unwise, however, to predict that all disturbed functions of the gonads can be regulated by administration of the incretions of the anterior lobe of the hypophysis. It must be remembered that the physiologic function intrinsic in the gonad must account for some of the major phenomena of the reproductive cycle.

With the development of these new tools it is reasonable to hope for the erection of a better structure than ever before. The expectation is justifiable that eventually a rational therapy will be developed. At present, however, attempts at therapeutic use of the knowledge obtained should be considered as experimental, and interpretation should be critical in order that the progress may continue.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—According to *Science*, Joseph Tannenberg, professor of pathology at the University of Frankfurt, has assumed the directorship of the Bender Hygienic Laboratory in Albany for one year, taking the place of Arthur W. Wright, who is now professor of pathology and bacteriology in the Albany Medical College.

Magnus Haaland, director of the Gade Pathological Institute in Bergen, Norway, and well known for his experimental studies on cancer in the first decade of this century, has died from coronary disease at the age of 59.

The George M. Kober Medal will be awarded to Frank B. Mallory, Boston, at the fiftieth annual meeting of the Association of American Physicians in Atlantic City, on May 7 and 8, 1935.

Society News.—The sixty-fourth annual meeting of the American Public Health Association will be held in Milwaukee, on Oct. 7 to 10, 1935.

Fellowships in Medicine of the National Research Council.—Fellowships in medicine, administered by the medical fellowship board of the National Research Council, are available for the year beginning July 1. These fellowships are open to citizens of the United States and Canada who possess an M.D. or Ph.D. degree. They are intended for recent graduates and not for persons already professionally established. The fellowships are designed to provide research discipline for men and women who are fitted for research in the medical sciences. At present candidates will be favored who plan to specialize in one of the sciences related to medicine or to approach clinical medicine and surgery through temporary identification with one of these sciences.

Bowman Cancer Fund.—For the present the income from the Bowman bequest to the University of Wisconsin is to be used for a series of special fellowships for research on cancer.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

SPORADIC CRETINISM IN ONE OF TWINS. GEORGE B. DORFF, Am. J. Dis. Child. **48**:1316, 1934.

A review of the literature reveals a case of sporadic cretinism in one of male twins (the other being normal) reported by Herrman, an atypical case in each of male twins reported by Manson, and a third case of suspected cretinism in each of twins reported by Petschacher. Two additional cases are presented in which sporadic cretinism occurred in two sets of differently sexed twins, one twin in each set being involved, the other twin being normal in all respects. For the first time definite roentgen evidence is given that the retarded osseous development in a twin with congenital sporadic cretinism occurred in utero. It is believed that (*a*) there is an independent low grade fetal thyroid activity which is not directly influenced by the maternal thyroid hormone; (*b*) there is probably no transmission of the thyroid hormone through the placenta from either the mother or the fetus. Stress is placed on the importance of studying the development of the bones in the new-born suspected of having hypothyroidism by roentgenograms.

AUTHOR'S SUMMARY.

THE RELATION OF AMIDOPYRIN AND ALLIED DRUGS TO THE ETIOLOGY OF AGRANULOCYTIC ANGINA. HENRY JACKSON, Am. J. M. Sc. **188**:482, 1934.

In 26 per cent of the cases of agranulocytosis studied the disease followed the administration of amidopyrine or allied drugs. That in these instances the disease may have been caused by the drugs is possible, perhaps probable. In 30 per cent of the cases the evidence shows that in spite of the fact that these drugs were taken in considerable quantities they had no causative relation to the disease. Forty-four per cent of the patients received no drugs of this type, yet the clinical and hematologic pictures were similar in every respect to those of patients who had taken these drugs.

FROM THE AUTHOR'S SUMMARY.

THE EXOPHTHALMOS OF GRAVES' DISEASE. DAVID MARINE and S. H. ROSEN, Am. J. M. Sc. **188**:565, 1934.

Chronic and progressive exophthalmos can now be readily produced in immature rabbits maintained on a diet of alfalfa hay and oats by injecting pituitary extracts or cyanide (preferably methyl cyanide). Production by both these means depends on two factors: (1) the presence of the thyrotropic hormone of the anterior lobe of the pituitary gland, in the one case supplied passively and in the other produced by stimulation of the pituitary gland, and (2) the existence of a relative thyroid insufficiency. The maintenance of a normal thyroid state by the administration of iodine or thyroxine prevents the exophthalmos that would otherwise be produced by the cyanide or by the pituitary extract. This indicates that normally there is a delicate physiologic balance between the thyroxine needs and the thyrotropic hormone. As regards therapy, iodine and desiccated thyroid gland appear to be the only logical remedies available at present, but neither in human exophthalmos nor in experimental exophthalmos of rabbits are the results promising.

AUTHORS' SUMMARY.

FIVE-YEAR SURVIVAL IN HODGKIN'S DISEASE. LLOYD F. CRAVER, Am. J. M. Sc. **188**:609, 1934.

Of 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3 per cent showed survival of the patients for five years or more following irradiation—of the proved

cases, 16.8 per cent. Five year survivors were, on the average, ten years younger (34 years of age) than a group that had survived for six months or less, though the extremes of age were the same in the two groups. The difference in the period of survival between the two groups is apparently due to a difference in the virulence of the disease. This, however, showed no correlation with the histologic appearance of the nodes removed at biopsy. Favorable features were: localization in one area, if combined with early thorough treatment; absence of leukocytosis or leukopenia; gain in weight after irradiation. Fever, marked pruritus and splenomegaly were apparently unfavorable signs.

AUTHOR'S SUMMARY.

CHRONIC CONGESTIVE SPLENOMEGALY AND ITS RELATIONSHIP TO BANTI'S DISEASE. RALPH C. LARRABEE, Am. J. M. Sc. **188**:745, 1934.

On the basis of a study of forty-seven cases the view is expressed that in the majority of patients presenting Banti's disease (splenomegaly with fibrosis, microcytic anemia with leukopenia and, in a late stage, hemorrhages and ascites) the condition is dependent on various intra-abdominal lesions obstructing the venous outflow of the spleen. By far the commonest of these is hepatic cirrhosis of various types. As Banti has limited the definition of the disease which bears his name in such a manner as to exclude conditions of the latter type it is thought best to segregate these under a distinctive name. However, splenectomy is indicated just as in Banti's disease, regardless of the nature of the underlying lesion.

AUTHOR'S SUMMARY.

ON THE INHERITANCE OF DIABETES MELLITUS. GREGORY PINCUS AND PRISCILLA WHITE, Am. J. M. Sc. **188**:782, 1934.

In a group of relatives of diabetic persons the blood sugar was determined and the sugar tolerance test was given. Approximately 14 per cent of those whose blood sugar was determined and 25 per cent of those given the sugar tolerance test had abnormally high blood sugar values as compared with similar determinations on control groups of normal healthy persons with no familial history of diabetes. When one examines the incidence of such "hyperglycemic" persons among the offspring of various types of matings, the data suggest that such persons may be taken as future diabetic patients, since the ratios of such persons among the offspring of these matings are approximately proportional to the ratios of presumed unidentified genetically diabetic persons called for by the mendelian hypothesis advanced to explain the inheritance of diabetes. These tests do not, however, reveal all the genetically diabetic persons. It is pointed out that if these tests have any general significance they indicate that the establishment of normal blood sugar values requires the strict exclusion of relatives of diabetic persons from the group of normal persons supplying the data.

AUTHORS' SUMMARY.

A FAMILIAL HEMORRHAGIC CONDITION SIMULATING HEMOPHILIA AND PURPURA HEMORRHAGICA. JASON E. FARBER, Am. J. M. Sc. **188**:815, 1934.

This study concerns five generations of a family totaling more than one hundred members twenty-five of which suffer from atypical pathologic hemorrhages. Fourteen (56 per cent) of these twenty-five members are males; eleven (44 per cent) are females. In regard to the males, the family tree has a striking similarity to that of hemophilic persons, but the affliction is essentially purpuric. The males have been more markedly involved, four of their number dying directly from hemorrhage. The hemorrhagic incidents are variable, but consist chiefly of prolonged frank bleeding from a cut or wound, ecchymoses and epistaxis in the males and menorrhagia and ecchymoses in the females. The coagulation time of the blood is normal; the bleeding time is intermittently prolonged; the platelets are numerically adequate, and the clot retracts normally; the chemistry of the

blood is normal. There seems to be no definite relation of the bleeding to season, diet, infection or occupation. Telangiectasis and splenomegaly are absent. Hypertension "runs in the family"; hemorrhages of the brain are frequent. No diagnosis is attempted; further studies are in progress.

AUTHOR'S SUMMARY.

FORMATION OF INTERCELLULAR SUBSTANCE BY THE ADMINISTRATION OF ASCORBIC ACID (VITAMIN C) IN EXPERIMENTAL SCORBUTUS. V. MENKIN, S. B. WOLBACH and M. F. MENKIN, Am. J. Path. **10**:569, 1934.

Ascorbic acid (vitamin C in crystalline form) administered orally or parenterally to scorbutic guinea-pigs induces reparative processes, as demonstrated by the renewal of dentin in the incisor teeth and by the deposition of osteoid matrix and chondromucin at the costochondral junction. These effects on the formation of intercellular substance are in accord with those previously obtained by Wolbach and Howe, feeding orange juice. They furnish additional support for the view that ascorbic acid is indistinguishable from vitamin C. The evidence obtained indicates that a relatively simple chemical substance, ascorbic acid, controls the deposition of intercellular substance. The possible mechanism involved in this reaction is discussed from the standpoint of the properties of ascorbic acid as a reducing agent in relation to cellular oxidations.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

THE FUNCTIONAL REACTIONS OF THE HUMAN THYROID. N. GOORMAGHTIGH and F. THOMAS, Am. J. Path. **10**:713, 1934.

A systematic histologic survey was made of a large series of human thyroid glands collected at autopsies in Ghent, Belgium, where endemic goiter is rare. In the normal thyroid gland, four types of epithelium were found: (1) the low cuboidal cell type, which secretes colloid slowly into the follicular cavity; (2) the large high cuboidal cell type, which secretes colloid actively; (3) the columnar type, which absorbs the stored colloid and excretes the hormone into the circulation, and finally (4) the endothelioid type, which is associated with a very slow secretion of colloid.

Under normal conditions the amount of stored colloid is kept fairly constant by the compensatory activity of columnar epithelium, on the one hand, and cuboidal epithelium, on the other. The cushion-like papillary proliferations (Sanderson) of the acinar wall are regarded as the result of functional stimulation of the excretory zone.

Under pathologic conditions, increased hormonal excretion into the circulation is compensated for by increased intrafollicular secretion. This compensated stage may last ten days. In cases of peritonitis following appendicitis, in intestinal obstruction and occasionally in diphtheria, there is evidence of an early decompensation, the excretion predominating over the intrafollicular storage.

C. A. HELLWIG.

THE RELATION OF INCREASED INTRA-ABDOMINAL PRESSURE TO THE LIVER LESIONS OF ECLAMPSIA. M. B. STRAUSS and S. MADDOCK, Am. J. Path. **10**:821, 1934.

Elevation of the intra-abdominal pressure according to the technic of Theobald was without effect on the livers of seven dogs anesthetized with ether. A chloroform-ether anesthetic mixture such as that employed by Theobald resulted in extensive central necrosis of the livers of three of four dogs, only two of which were subjected to increases of intra-abdominal pressure. The theory that the hepatic lesions of eclampsia are due to increased intra-abdominal pressure, although an attractive one, must be considered as unproved.

FROM THE AUTHORS' SUMMARY.

HYPERPARATHYROIDISM DUE TO DIFFUSE PARATHYROID HYPERPLASIA. F. ALBRIGHT, E. BLOOMBERG, B. CASTLEMAN and E. D. CHURCHILL, Arch. Int. Med. **54**:315, 1934.

Three patients with hyperparathyroidism were found to have hyperplasia of all the parathyroid glands. The structure of the glands differed markedly from that when there is enlargement of only one parathyroid gland. The distinctive features were the uniformity of structure, the enormous size of the cells, the extreme clearness of the cytoplasm and the tendency to gland formation. A distinction is made between parathyroid hyperplasia with hyperparathyroidism and compensatory hyperplasia of the parathyroid glands. An analogy between the former and exophthalmic goiter is made. Hyperplasia of the parathyroid glands with hyperparathyroidism is considered as an entity. The surgical treatment of this condition brings up some interesting questions. Thus, removal of two enlarged glands in one of these patients was without effect on the levels of the blood calcium and inorganic phosphorus. Even with removal of sufficient tissue to alter the blood chemistry the condition may recur. A review of 101 cases of hyperparathyroidism revealed 17 cases, including these 3, in which there was general parathyroid enlargement. The cause of the hyperplasia may be a parathyroid-stimulating factor, possibly from the hypophysis.

FROM THE AUTHORS' SUMMARY.

SPIDER POISONING (LATRODECTUS MACTANS). A. W. BLAIR, Arch. Int. Med. **54**:831 and 844, 1934.

The venom of the adult female spider Latrodectus mactans is dangerously poisonous to man. The development of the clinical picture may be divided into three stages, the second of which, that of shock, is the most critical. The sequence of symptoms is sufficiently characteristic to entitle it to recognition as a clinical entity in the field of general medicine.

Latrodectus mactans is the only spider found in the United States that has been proved to be poisonous. No complete study of its life history has hitherto been made, however. For the past two years a study of this spider as found in the vicinity of Tuscaloosa, Ala., has been made. Observations, accompanied by illustrations, on its appearance, habitat, web, feeding habits, mating, egg sac, eggs, development, span of life and danger to man are presented.

FROM THE AUTHOR'S SUMMARIES.

NEUROGENIC EROSIONS AND PERFORATIONS OF THE STOMACH AND ESOPHAGUS. M. G. MASTEN and R. C. BUNTS, Arch. Int. Med. **54**:916, 1934.

Masten and Bunts report six cases of lesions in the brain associated with erosions and perforations of the upper part of the gastro-intestinal tract. These cases support the hypothesis advanced by Cushing that gastromalacia and ulcers of the upper part of the gastro-intestinal tract may be related to disease of the interbrain and caused by parasympathetic stimulation. They bring forward experimental evidence as to the location of the parasympathetic and sympathetic centers of the interbrain.

INFLUENCE OF BLADDER TRANSPLANTS ON THE HEALING OF DEFECTS OF BONE. G. H. COPHER and J. A. KEY, Arch. Surg. **29**:64, 1934.

In attempting to bridge defects in the dog's ulna after excision of 1 cm., the observation of Huggins that the epithelium of the urinary bladder influences the formation of bone was applied. One ulna was used for a control; in the defect of the other mucosa from the bladder of the same dog was inserted. Of sixteen dogs, twelve showed union of the side with the transplant, while in only two of the controls did union take place. New bone formation was present in only three of the controls but was seen in all of the dogs in which transplants were used.

It seemed that the new bone formed adjacent to the mucosa of the bladder and directly in connective tissue but was not preceded by formation of cartilage.

T. D. ROBERTSON.

EFFECT OF PARATHYROID EXTRACT ON THE KIDNEY AND BLOOD IN MAN. R. ELLSWORTH and J. E. HOWARD, Bull. Johns Hopkins Hosp. **55**:296, 1934.

The intravenous injection of 40 units of parathyroid extract into normal persons is followed by an immediate outpouring of phosphorus in the urine. In some instances there was a diuresis, but in others this did not occur. The urea clearance was not markedly altered; the excretion of chloride was diminished rather than augmented; the p_H of the urine tended to shift to a more alkaline range. There was a relatively slight fall in plasma inorganic phosphorus. The serum calcium in several instances, instead of rising, tended to fall. The theoretical implications of these findings are briefly discussed. FROM THE AUTHORS' SUMMARY.

BIOLOGIC EFFECTS OF THYMUS EXTRACT. L. G. ROWNTREE, J. H. CLARK and A. M. HANSON, J. A. M. A. **103**:1425, 1934.

Thymus extract (Hanson) accelerated the rate of growth and development and hastened the onset of adolescence in the offspring of treated rats, and seemed to increase the fertility of parent rats. The injection of thymus extract into parent rats in succeeding generations resulted in an amplification of the effects of the thymus extract.

AUTHORS' SUMMARY.

STUDIES ON ORGANOGENESIS. R. C. PARKER, J. Exper. Med. **60**:351, 1934.

Isolated blood cells, when incubated in a plasma substratum, are capable of constructing highly organized tubular processes that project from the explanted cell mass into the surrounding medium. The tubular structures have fibrillar walls that may be covered eventually by a membranous layer of leukocytes. Their lumens contain blood cells suspended in fluid. The formation of the tubules is initiated by the red cells. The leukocytes, more particularly the thrombocytes, are responsible for the construction of the walls. The phenomenon occurs only in the presence of plasma the coagulation of which has been slightly delayed. Once the surrounding medium has become firmly coagulated, no further change occurs in the length or in the diameter of the tubules. The development of the tubules is not suppressed by substances that enhance cellular activity unless they induce, at the same time, immediate coagulation of the medium. The addition of the juice of embryo tissue prevents the formation of these structures by producing early coagulation. The phenomenon as a whole is dependent on the physicochemical nature of the medium, the character and thickness of the explanted fragment and the physical peculiarities of the cells that comprise it. It is the expression of various physicochemical and physiologic events that have occurred in a definite order or sequence.

FROM THE AUTHOR'S SUMMARY.

THE METABOLISM OF COPPER AND IRON IN SPLENECTOMIZED RATS FREE FROM BARTONELLA MURIS INFECTION. M. SANDBERG and D. PERLA, J. Exper. Med. **60**:395, 1934.

In albino rats free from infection with Bartonella muris removal of the spleen is followed by an increased elimination of copper in the feces, which commences two weeks after splenectomy, the metabolism of iron returning to normal after this period. No disturbance in the metabolism of creatine or creatinine occurs. The amount of uric acid is unchanged. There is an increase in the nitrogen retained, first noted three weeks after splenectomy. The spleen is essential for the utilization of copper in the body. FROM THE AUTHORS' SUMMARY.

A Factor Increasing Tissue Permeability in Organs Other Than the Testicle. A. Claude and F. Duran-Reynals, J. Exper. Med. **60**:457, 1934.

Many of the organs from animals of both sexes, including the ovary, have been found to contain in various proportions a factor or factors increasing the permeability of the tissue. The potency exhibited by such active extracts was always less than that of extracts from the testicle. Blood serum was found to be devoid of any spreading property.

From the Authors' Summary.

The Participation of Skin Lymphatics in the Repair of Lesions Due to Incisions and Burns. P. D. McMaster and S. S. Hudack, J. Exper. Med. **60**:479, 1934.

With the aid of solutions of vital dyes, the lymphatic capillaries in the ear of the mouse have been studied during the period of immediate reaction to injuries of various sorts and during the period of repair. The behavior of lymphatics severed by incision differs greatly from that of small blood vessels. Instead of closing they sometimes remain open for as long as forty-eight hours. Materials introduced into the wound pass directly into the lymphatics through their gaping ends, a fact which will explain why infection from incisions is predominantly along the lymphatics. All around an injury the lymphatics are rendered abnormally permeable. So, too, are the blood vessels, a fact well recognized in the past. From twenty-four to forty-eight hours later, at a time when the blood vessels in the edematous tissue surrounding the injured area are still much more permeable than normal, the draining lymphatics allow far less to escape than usual. The possible reasons for this have been discussed. The lymphatics participate in the removal of fluid from the edematous tissue. As repair after injury takes place severed lymphatics may reunite when as yet there are no functioning blood vessels. Later an active hyperplasia of the lymphatic channels occurs, with budding of an extraordinarily abundant plexus of minute lymph capillaries into the area under repair.

From the Authors' Summary.

Irreversible Character of the Late Changes after Hepatectomy. P. D. McMaster and D. R. Drury, J. Exper. Med. **60**:503, 1934.

The symptoms of advanced hepatic insufficiency in the hepatectomized rabbit are irreversible. That is to say, cross-transfusions between liverless rabbits and normal ones fail to ameliorate the symptoms of deprivation of liver once they are established. The normal rabbits show no symptoms suggesting that toxic substances have accumulated in the blood of the hepatectomized ones.

From the Authors' Summary.

Metabolic Effects of Host Constitution in Mouse Leukemia. J. Victor and J. S. Potter, J. Exper. Med. **60**:547, 1934.

The genetic constitution of the host modifies the metabolism of the cell line. The same host constitution may modify the metabolism of different cell lines in different ways. The constitution of the host does not appear to modify the inherent constitution of the leukemic cells, but acts on their metabolism as a determining environmental factor.

From the Authors' Summary.

Pathologic Anatomy

Thrombosis and Pulmonary Embolism. T. H. Belt, Am. J. Path. **10**: 129, 1934.

Pulmonary embolism is to be observed in approximately 10 per cent of autopsies on adult persons and is much commoner in medical than in surgical cases. In more than half of the cases there are infarcts of the lungs, and in nearly all there are repeated embolisms occurring over a period of hours, days or weeks.

Thromboses of leg and pelvic veins are the chief source of dangerous pulmonary emboli. Such thromboses commonly develop without clinical manifestations, and no evidence of active inflammation is shown in the adjacent wall of the vein. The dangerous type of thrombosis has a high incidence in cases of cardiac insufficiency. From the work of Blumgart and Weiss it is evident that the flow of blood in the veins is slowed when the heart's function is impaired, and slowing of the blood stream is known to favor thrombosis. Other factors seeming of lesser significance in the present series of cases, I regard circulatory embarrassment as of prime importance in the etiology of venous thrombosis and pulmonary embolism. A high percentage of postoperative fatalities from pulmonary embolism show evidence of minor degrees of cardiac incompetence.

FROM THE AUTHOR'S SUMMARY AND CONCLUSIONS.

THE PATHOLOGIC ANATOMY OF THE LIVER IN EXOPHTHALMIC GOITER. D. C. BEAVER and J. DEJ. PEMBERTON, Ann. Int. Med. **7**:687, 1933.

The pathologic anatomy of the liver and the correlated clinical findings in 107 cases of exophthalmic goiter are recorded. There are three types of hepatic lesions: (1) acute degeneration (fatty metamorphosis, focal and central necrosis and changes secondary to vascular stasis); (2) simple atrophy; (3) subacute toxic atrophy and toxic cirrhosis. The incidence of these lesions was as follows: (1) acute lesions—95 per cent, of which fatty changes composed 87.8 per cent; (2) atrophy—63.55 per cent, with an average hepatic weight of 1,316 Gm.; (3) subacute toxic atrophy and cirrhosis—59.81 per cent. Jaundice occurred in 21.5 per cent. The basic factor in all these lesions appears to be the severity of the syndrome of exophthalmic goiter. The hepatic lesions appear to be an integral part of the syndrome and due directly to thyroid intoxication. JACOB KLEIN.

JUVENILE ELASTOSIS. FRED D. WEIDMAN, N. P. ANDERSON and S. AYRES, Arch. Dermat. & Syph. **28**:182, 1933.

A child, aged 5½ years, presented nodular lesions on the trunk, buttocks and thighs, of a color varying from flesh tone to ivory white and pink. Section showed marked elastosis.

VITILIGO. S. W. BECKER, Arch. Dermat. & Syph. **28**:497, 1933.

Study of sections at the border of vitiliginous patches showed that in the depigmented portion only the small clear cells (*cellules claires*) of Masson are found. In the pigmented portion large dendritic pigment-containing cells are seen, which have the same location and staining characteristics as the clear cells. It is therefore evident that enlargement and pigment formation are associated functions of these cells. In recent patches of vitiligo a few dendritic pigment-containing melanoblasts were found, but in old patches only the small clear cells were present. This seems to explain the different results of different authors in treating patients by the same methods. Studies of sections from patches of pinta by pigment methods showed that the process begins as an inflammatory one with pigment activity, followed by a most marked deposition of melanin in histiocytes in the superficial dermis. This accounts for the blue stage of pinta. This is followed later by complete depigmentation. In the depigmented patches of pinta practically no clear cells could be seen. AUTHOR'S SUMMARY.

FAT IN THE CELLS OF TISSUE CULTURES. K. HASZLER, Beitr. z. path. Anat. u. z. allg. Path. **92**:101, 1933.

Fat appears in the fibroblasts of tissue cultures. It is the result of specific cellular metabolic activities. The fat of the substrate may be phagocytosed and burned by the cell. The formation of fat from sugar could not be demonstrated.

O. T. SCHULTZ.

FAT EMBOLISM OF THE LUNGS. L. JANKOVICZ, Beitr. z. path. anat. u. z. allg. Path. **92**:110, 1933.

In thirty-one casualty fatalities, fat embolism of the lungs was observed as long as fourteen days after the accident, if the victim lived that long or longer. Resorption of the fat from the lungs is not due to cellular activity but to ferment action which takes place in the capillaries.

O. T. SCHULTZ.

MELANOSIS OF THE COLON DUE TO BISMUTH. G. MICSEH, Beitr. z. path. Anat. u. z. allg. Path. **92**:146, 1933.

Micseh describes the gross and histologic changes in two cases of melanosis of the colon due to bismuth. The patients had received injections of bismuth compounds in the treatment of syphilis. The finely granular, brownish-black pigment, which was situated chiefly in the capillary endothelium of the mucosa, gave the chemical reactions of bismuth.

O. T. SCHULTZ.

HEMORRHAGIC AGRANULOCYTOSIS. E. NACHTNEBEL, Beitr. z. path. Anat. u. z. allg. Path. **92**:156, 1933.

Under the name "aleukia haemorrhagica" Nachtnebel reports three cases of agranulocytosis in which hemorrhage was a feature. In two cases there was marked aplasia of the bone marrow. The patients were receiving treatment with arsphenamine for syphilis when the terminal illness developed. He ascribes the changes in the bone marrow, to which sepsis was secondary, to the action of arsenic. In the third case sepsis was the primary factor. Massive roentgen irradiation of the long bones of dogs led to a condition clinically and anatomically similar to human agranulocytosis.

O. T. SCHULTZ.

DIFFUSE SYPHILIS OF BONE. H. REMÉ, Beitr. z. path. Anat. u. z. allg. Path. **92**:290, 1933.

In two cases of diffuse syphilitic osteitis, microscopic examination revealed areas of alternate bone resorption and bone formation along the haversian canals and on the bone trabeculae. This process had resulted in the formation of the mosaic bone that Schmorl has considered characteristic of Paget's osteitis deformans. From his findings Remé holds that mosaic structure cannot be considered histologically characteristic of osteitis deformans, and that assertions of the frequency of Paget's disease in prehistoric bones may not be warranted. The differentiation between osteitis deformans and syphilis must rest on the greater degree of periosteal involvement in syphilitic osteitis; this process may not be detectable in dried bones.

O. T. SCHULTZ.

MYOCARDIAL NECROSIS DUE TO CORONARY INSUFFICIENCY. F. BÜCHNER, Beitr. z. path. Anat. u. z. allg. Path. **92**:311, 1933.

In four hearts with deficient coronary circulation as the result of coronary or aortic disease, from persons who during life had had attacks of angina pectoris on exertion, there were observed multiple small necroses of the inner layer of the myocardium and of the papillary muscles of the left ventricle. These lesions, which are termed "the morphologic substrate of angina pectoris", were held to be the result of ischemia due to insufficiency of the coronary circulation during sudden exertion. The findings are interpreted as confirmatory of Mackenzie's view that the pain of angina pectoris is due to muscular ischemia. To determine experimentally whether sudden insufficiency of the coronary circulation could produce such myocardial necroses, rabbits that had been kept quiet in individual cages were rendered acutely anemic by a single bleeding from the ear vein. From fifteen minutes to one hour later they were placed in an electrically driven treadmill. The animals became exhausted in from five to seventeen minutes, and three died

within a half hour. The remaining animals, five in number, were killed at intervals of seven, ten and twenty hours and five and eight days. The myocardium of the left ventricle was examined histologically for necroses. No changes were detected in the animals that died from the exertion of the treadmill. All the remaining rabbits revealed multiple necroses of the myocardium, with fibroblastic reparative changes in those animals that were allowed to survive longest. Control animals that were killed at intervals after bleeding revealed no myocardial necroses.

O. T. SCHULTZ.

EXCRETION OF LIPOIDS BY THE LUNGS. E. JECKELN, Beitr. z. path. Anat. u. z. allg. Path. **92**:357, 1933.

Microscopic examination of the lungs of a child, aged 6 years, who died of lymphoid leukemia revealed the presence of striking amounts of lipoid material in the interalveolar capillaries and alveolar spaces. The material occurred in the form of fine droplets, granules and larger masses; some of it was contained in alveolar phagocytes. It was present in largest amount in the capillaries of those parts of the lungs in which the alveoli were filled with lymphocytes or erythrocytes. To study the fate of fat in the lungs, milk and olive oil were introduced intratracheally into rabbits. From the experiments and from the study of the human material, Jeckeln interprets the unusual findings in the case of leukemia as evidence of excretion of lipoids by the lungs. He postulates that the child had lipemia; it is to be noted that such a state of the blood was not detected during life. In the lung capillaries, probably through enzymatic action, the lipoid material was partly saponified, subdivided, emulsified, excreted into the alveoli and removed in the sputum. Where excretion into the alveoli was interfered with by filling of the air spaces with cellular or hemorrhagic exudate the capillaries contained the largest amounts of the material.

O. T. SCHULTZ.

THE PATHOLOGIC ANATOMY OF INJURIES TO THE LUNGS. L. M. EIDLIN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:445, 1934.

At the place of injury or hemorrhage in the lung appear early large cells which take up red cells. These cells appear to arise from the alveolar epithelium. Histiocytes and endothelial cells do not seem to take part in the phagocytosis of red cells.

BENIGN NEPHROSCLEROSIS AND ARTERIAL HYPERTENSION. P. KIMMELSTIEL, Virchows Arch. f. Path. Anat. **290**:245, 1933.

The kidneys of persons who had had arterial hypertension during life were perfused with physiologic solution of sodium chloride as soon after death as possible. Normal human kidneys, secondarily contracted kidneys and kidneys showing malignant nephrosclerosis were perfused in the same way. The perfusion time for a unit volume of liquid was correlated with the histologic changes in the kidney. The occurrence of essential hypertension without recognizable vascular alterations is accepted. With increasing age hyperpiesis becomes associated with arterial and arteriolar sclerosis of the renal vessels. At a certain degree of arterial involvement the perfusion time was found to be increased. This critical point is characterized histologically by disappearance of parenchyma and functionally by latent renal insufficiency.

O. T. SCHULTZ.

ATYPICAL AMYLOIDOSIS. BERTEL VON BONSDORFF, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:369, 1933.

A detailed clinical, pathologic and biochemical study is reported of atypical amyloidosis as it occurred in a 51 year old man whose illness began from two to three months after the fracture of a rib and terminated fatally one and a half years later. Large, firm, symmetrical swellings developed in the vicinity of the

large joints and on the tongue. Microscopically the swellings were amyloid in nature. Biochemical examination demonstrated a disturbance in the metabolism of albumin. The plasma protein fraction showed a preponderance of fibrin and globulin. Bence-Jones protein was not found. The amyloid substance acted like a foreign body; giant cells were frequently found at the periphery of such an accumulation. There was no evidence of multiple myeloma. Multiple myeloma may occur without amyloid formation, and atypical amyloidosis may occur without myeloma. Von Bonsdorff believes that classic as well as atypical amyloidosis is due to a disturbance in the metabolism of albumin. Pathologic changes in the bones predispose to a diffuse amyloidosis. The etiologic relation of trauma is discussed, and numerous cases are cited from the literature which tend to indicate a causative relation between bone trauma and amyloidosis.

JACOB KLEIN.

INFLAMMATORY REACTION IN THE OMENTUM. P. E. A. NYLANDER, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:453, 1933.

The inflammatory response of the omentum was studied microscopically in a series of 100 appendectomies. Mere eventration of the omentum during the course of operation was sufficient to cause definite inflammation after ten minutes. In acute appendicitis the omentum showed a preponderance of polymorphonuclear cells in the inflammatory reaction. The macrophages were next in frequency, while the lymphocytes and plasma cells were scarce. In peritonitis the polymorphonuclear cells predominated during the first twenty-four to forty-eight hours; afterward the monocytes were more numerous. In several fatal cases of peritonitis following appendical perforation there was no noteworthy inflammatory reaction in the omentum. This may indicate a poor resistance or an overwhelming infection. In interval appendectomies it was observed that the omentum displayed a marked ability to return to normal. No noteworthy differences in the inflammatory response were observed in relation to age or sex. The defensive function of the omentum depends on the activity of the neutrophils. Macrophages, mesothelial cells and lymphocytes are of secondary importance.

JACOB KLEIN.

ENDOMETRIOSIS ESPECIALLY REGARDING LOCALISATION IN THE ABDOMINAL WALL (LAPAROTOMY SCARS), WITH A STUDY OF EXPERIMENTAL TRANSPLANTATION OF ENDOMETRIUM. H. F. HARBITZ, Acta chir. Scandinav., supp. 30, p. 1, 1934.

In the first part of the work the history of endometriosis is reviewed, especially the chief theories that have been advanced respecting the pathogenesis of the disease. These are: development through outgrowth from uterine or tubal mucosa, origin from fetal remnants of the wolffian body (the wolffian theory of von Recklinghausen), derivation from serosal epithelium (R. Meyer) or from persistent cells with the properties of the celomic epithelium, metastatic origin through lymphatic or venous channels, and occurrence owing to implantation of differentiated müllerian tissue (Sampson's theory). It is especially the seroso-epithelial theory and the implantation theory that stand in sharp opposition to each other at present. I have dealt at some length with Sampson's theory, which seems to have much in its favor, particularly on account of the experiments made in late years in transplantation and explanation of endometrium.

Further there is given a short account of the most important clinical features and chief localizations of endometriosis: in the genital organs, in other parts of the peritoneal cavity and, extraperitoneally, in the groin, navel, laparotomy scars and perineum. Especially the last named localizations are of interest in this work. An endeavor is made to bring forward clinical facts that may be taken to support the view that endometriosis in these localizations has arisen through continuous outgrowth or through implantation of differentiated müllerian tissue.

On the basis of my own cases I have discussed the not infrequent occurrence of inguinal endometriosis in combination with hernias of different kinds, and the

simultaneous appearance of inguinal endometriosis and intraperitoneal endometrial growths, as well as the combination of inguinal endometriosis with endometriosis in laparotomy scars in the same region. The occurrence of all these combinations seems to speak for the assumption that inguinal endometriosis may arise through outgrowth or through implantation.

As regards endometriosis in the navel, the same combination with a hernia or with a laparotomy scar may be encountered. Further it is pointed out that on the posterior aspect of the umbilicus there are very often found peritoneal pouches, which must be supposed to favor the reception and implantation of endometrial particles.

The second part of the work deals with endometriosis in laparotomy scars (and in the perineum). On the basis of fifteen cases of my own, and also of instances collected from the literature, I have made an analysis of this particular localization of endometriosis, especially in order to cast light on the pathogenesis. It will here be sufficient to refer to the summary at the end of the chapter (p. 222).

The third part treats of experimental transplantation of endometrium in rabbits, including transplantations in the abdominal wall and in laparotomy scars. Also here I confine myself to referring to the summary at the end of the chapter (p. 361).

Through this combination of theoretical examination of the implantation theory with clinical analysis, particularly of endometriosis in the abdominal wall, and through experiments in transplantation of endometrium, it has been my object to show the probability of the origin of the disease, at all events of extraperitoneal endometriosis in the abdominal wall, from differentiated müllerian tissue through continuous outgrowth or through implantation. FROM AUTHOR'S SUMMARY.

SUDDEN DEATH FROM OBSTRUCTION OF THE MITRAL ORIFICE BY AN AURICULAR THROMBUS. NILS LIEDBERG, Acta path. et microbiol. Scandinav., supp. 16, p. 219, 1933.

Two cases of sudden death from mitral stenosis are reported. In one the mitral orifice was closed by a ball thrombus from the auricle. In the other polypoid extension of a mural thrombus in the left auricle occluded the orifice. The clinical resemblance to pulmonary embolism is pointed out. JACOB KLEIN.

MAST CELLS. U. QUENSEL, Acta path. et microbiol. Scandinav., supp. 16, p. 358, 1933.

Mast cells are found in connective tissue and the blood; also in the thymus in increasing numbers with increasing age. In diameter they vary from 8 to 37 microns, and are actively ameboid. Their function is to secrete mucin for the interfibrillar substance of connective tissue. Ehrlich described them as the nonphagocytic nutritive wandering cells. JACOB KLEIN.

STRUCTURAL CHANGES IN SWEDISH CASES OF JUVENILE AMAUROTIC IDIOCY. EINAR SJÖVALL and ERIC ERICSSON, Acta path. et microbiol. Scandinav., supp. 16, p. 460, 1933.

This report concerns anatomic studies on nineteen cases of juvenile amaurotic idiocy. The morphologic changes have shown surprising uniformity. There was constant involvement of the neostriatum associated with lipoid deposits and macroglial changes. The latter also occurred in the cerebral as well as the cerebellar cortex independently of the lipoid deposits in the ganglion cells. Other findings, such as degeneration of ganglion cells, atrophy of myelin sheaths and fibrogliosis, agree with changes in normal senescence. The authors conclude that in amaurotic idiocy there is a precocious senescence due to disturbance of lipoid metabolism. JACOB KLEIN.

SPONTANEOUS HYPOGLYCEMIA. THOR STENSTRÖM and HELGE SJÖVALL, Acta path. et microbiol. Scandinav., supp. 16, p. 484, 1933.

A 35 year old woman, whose blood had a sugar content of 0.035 Gm. per hundred cubic centimeters, died after a period of illness with weakness, loss of appetite, headache and mental disturbances. The anatomic study demonstrated fibrosis and atrophy of the hypophysis, atrophy and sclerosis of the thyroid gland, atrophy of the suprarenal glands and premature involution of the ovaries. Small arteries in all the organs, especially the kidneys, showed sclerosis, fatty change and endarteritis. The authors suggest the possibility of a toxic disturbance of the blood vessels as the cause. There are a review and discussion of the pertinent literature.

JACOB KLEIN.

Microbiology and Parasitology

RHEUMATIC HEART DISEASE AT ONE YEAR. VINCENT E. FISCHER, Am. J. Dis. Child. **48**:590, 1934.

Rheumatic heart disease, established by postmortem examination, is described in an infant 12½ months old, whose mother had acute rheumatic fever from the third to the seventh month of its fetal life.

FROM THE AUTHOR'S SUMMARY.

VARIETIES OF TYPHUS VIRUS AND THE EPIDEMIOLOGY OF THE AMERICAN FORM OF EUROPEAN TYPHUS FEVER (BRILL'S DISEASE). H. ZINSSER, Am. J. Hyg. **20**:513, 1934.

Brill's disease is an imported form of the classic European typhus fever. The cases observed in New York and Boston represent recrudescences of old infections originally acquired in European foci. In communities not heavily louse-infested such cases remain sporadic, but in louse-infested and crowded areas they may furnish foci for the origin of small or large outbreaks. They may thus serve to maintain endemic prevalence by bridging breaks in the chain of man-louse-man propagation. It is suggested that this is the manner in which the European virus has been maintained in continental foci for centuries. Rat reservoirs are thus not necessary for the endemic continuance of the disease, though they probably coexist.

FROM THE AUTHOR'S SUMMARY.

ON AIR-BORNE INFECTION (VIABILITY OF DROPLET NUCLEI INFECTION). W. F. WELLS and W. R. STONE, Am. J. Hyg. **20**:619, 1934.

With all speculation disregarded and the limitations of the experiments, the volume of data and the circumstances of control recognized, it seems to be demonstrated that bacteria can remain suspended alive in the air for periods which may permit their wide dissemination. It also seems obvious that the time and distance droplet nuclei infection may travel depend more on the viability of the micro-organisms in air than on their settling rate. Important differences in viability in air of micro-organisms are apparent, and these differences seem to be consistent with the etiology, epidemiology and pathology of air-borne infection. Without attempting to interpret these facts in terms of epidemiology, the need of further study of bacterial behavior in air is brought forward.

FROM THE AUTHORS' SUMMARY.

HUMAN INFECTION CAUSED BY A YEAST-LIKE ORGANISM OF GENUS SEPEDONIUM. G. H. HANSMANN and J. R. SCHENKEN, Am. J. Path. **10**:731, 1934.

In lesions of the skin and in the lymph nodes a yeastlike organism was found, which was isolated in pure culture, and in which large spiculated chlamydospores developed on lateral branches of a delicate mycelium. This appears to be the first case of its kind.

EFFECTS OF VACCINES AND OF BACTERIAL AND PARASITIC INFECTIONS ON EOSINOPHILIA IN TRICHINOUS ANIMALS. WESLEY W. SPINK, Arch. Int. Med. **54**:805, 1934.

The number of circulating eosinophilic leukocytes in animals infected with Trichinella spiralis was reduced following infection with Bacillus tuberculosis, Staphylococcus aureus and Trypanosoma equiperdum. Animals which had received repeated injections of typhoid vaccine responded with a rise in the number of eosinophilic leukocytes. No change was noted following the injection of heat-killed tubercle bacilli. Studies of the bone marrow from the same animals did not reveal a corresponding decrease in the number of eosinophilic cells. Trichinous animals having a superimposed tuberculosis or trypanosomiasis had less reaction around the encysted parasites in the muscle than the control animals. Trichinous animals inoculated with typhoid vaccine showed similar changes in the muscles. Trichinous animals subjected to a high degree of dry heat responded with an absolute rise in the number of circulating eosinophilic leukocytes. No relationship was found between the weight of an animal and the level of eosinophilic leukocytes in its peripheral blood. The number of circulating eosinophilic cells did not appear to be related to the mode of encystment of Trichinella spiralis in the muscle.

AUTHOR'S SUMMARY.

ETIOLOGY OF THE 1933 EPIDEMIC OF ENCEPHALITIS. R. S. MUCKENFUSS, C. ARMSTRONG and L. T. WEBSTER, J. A. M. A. **103**:731, 1934.

A number of strains of a virus that seems to have been the etiologic agent of the 1933 epidemic of encephalitis were isolated in two different laboratories. This virus acts on monkeys and white mice and is distinct from previously known viruses. The number of strains of similar characteristics isolated and the neutralization of the virus by the serum of persons convalescent from encephalitis in this epidemic, but not by the serum of persons recovered from other diseases, justify the conclusion that it was the etiologic agent of the recent epidemic.

INHALED SILICA AND ITS EFFECT ON NORMAL AND TUBERCULOUS LUNGS. L. U. GARDNER, J. A. M. A. **103**:743, 1934.

Dusts containing silica are preeminently dangerous. Present knowledge will not permit it to be said that only free silica is harmful; possibly some of the silicates will also be incriminated. One silicate, asbestos, produces a characteristic and dangerous type of pulmonary fibrosis. Silica is a poison to the tissues. In low dilutions it causes nodular fibrosis; in higher concentrations it produces rapid necrosis of cells of all kinds. Human silicosis begins by damaging the pulmonary lymphatic apparatus and progresses by the development of nodular fibrosis of the parenchyma of the lungs. Silicosis specifically predisposes to infection with the tubercle bacillus. The mechanism of this action has not yet been determined. It probably consists in some alteration in the soil rather than in changes induced in the infecting organism. Nonsiliceous dusts inhaled in combination with silica modify the action of the latter, altering the anatomic characteristics of the lesions and apparently decreasing the susceptibility to tuberculosis.

FROM THE AUTHOR'S SUMMARY.

THE ST. LOUIS TYPE OF ENCEPHALITIS. H. A. MCCORDOCK, W. COLLIER and S. H. GRAY, J. A. M. A. **103**:822, 1934.

The essential pathologic process in the St. Louis type of encephalitis is a nonsuppurative inflammation of the nervous system characterized by intense vascular congestion, cellular infiltration and degenerative changes in the nerve cells. Severe examples of the disease which closely resemble the Japanese type B can readily be distinguished from the lethargic type, although the milder cases cannot be differentiated from the latter on the basis of the pathologic lesions alone.

FROM THE AUTHORS' SUMMARY.

A Partial Purification of Yellow Fever Virus Through Adsorption and Elution. T. P. Hughes, J. Bact. **28**:401, 1934.

Preparations of yellow fever virus have been made possessing a high degree of activity and having a protein content at least fifty times less than can be demonstrated by chemical tests for protein. The method used is that of adsorption on kaolin followed by selective elution with dilute ammonia. This partial purification can be accomplished with ease and rapidity. From the Author's Summary.

The Virus of Brill's Disease. S. R. Savoor and R. Velasco, J. Exper. Med. **60**:317, 1934.

The experiments described have confirmed the observations of Laigret and Jadin that the virus of the European human typhus cannot be maintained for more than two generations in mice by brain-peritoneum passage, whereas the murine Mexican variety can be carried on by this method in mice through at least eleven passage generations. The fact that within eleven passages there is no attenuation of the murine virus renders it likely that this agent can continue in mice in an unapparent form without material modification. The virus of Brill's disease from three different isolations has behaved like the European type, a fact which strengthens the opinion previously expressed in articles from this laboratory that Brill's disease represents an imported strain of the classic European infection.

From the Authors' Summary.

Spontaneous Conjunctival Folliculosis. P. K. Olitsky, J. T. Syverton and J. R. Tyler, J. Exper. Med. **60**:375, 1934.

It appears that in three types, at least, of follicular reactions in the conjunctiva —that in man (the primary lesion of trachoma consisting essentially of follicles), that in the simian and that in the rabbit—there is an intimate association of micro-organisms having the same generic but different specific properties.

From the Authors' Summary.

Whooping Cough: Type-Specific (S) and Dissociation (R) Forms of Hemophilus Pertussis. G. S. Shibley and H. Hoelscher, J. Exper. Med. **60**:403, 1934.

Fifty-nine recently isolated strains of Haemophilus pertussis and thirty-nine from laboratory stock have been studied with respect to their cultural, morphologic, toxic, serologic and cataphoretic properties. The recently isolated strains, whether derived from cases of whooping cough in Europe or in this country, are all of a single specific serologic type which should be designated as the S form of H. pertussis. Criteria for the identification of the S form are given. The S form may be maintained in this stage by suitable cultural methods. If grown on mediums deficient in blood, it will dissociate into an antigenically different form, which should be designated the R form in keeping with the current terminology employed in describing bacterial dissociants. From the Authors' Summary.

Biologic Studies of the Tubercle Bacillus. W. Steenken Jr., W. H. Oatway Jr. and S. A. Petroff, J. Exper. Med. **60**:515, 1934.

The H_{37} strain of human tubercle bacillus has been dissociated into two variants: the R, or avirulent, and the S, or virulent. When their dissociation is complete, the colony morphology of each is distinctive and typical. The morphology of the individual bacilli of the two variants is different and characteristic. The R variant develops best in an acid medium; the S, in an alkaline medium. A method of assortment to facilitate the procedure of forced dissociation has been described. The difference in virulence has been proved by observations on the pathogenesis of the variants.

From the Authors' Summary.

THE PROTECTION OF COPPER AGAINST TRYPANOSOMA EQUIPERDUM IN RATS. D. PERLA, J. Exper. Med. **60**:541, 1934.

Copper in amounts equivalent to 0.2 mg. of elemental copper per rat per day during a period of ten days prior to induced infection with small numbers of trypanosomes raised the natural resistance of the rats to the infection. The infection was aborted in all instances when the rats were infected by the injection of 2,000 trypanosomes and in 75 per cent of instances when the rats were infected by the injection of 10,000 trypanosomes. FROM THE AUTHOR'S SUMMARY.

THE MECHANISM OF INVASIVENESS OF STREPTOCOCCI. E. W. DENNIS and D. BERBERIAN, J. Exper. Med. **60**:581, 1934.

Menkin's observations of the failure of inflammatory fixation in areas of acute inflammation due to Streptococcus haemolyticus have been confirmed. The lack of inflammatory fixation in the presence of streptococci is not due to the passive nature of these organisms, but may be attributed to the production of (1) fibrinolytic and (2) antifibrinogenic substances which dissolve the fibrin barrier or prevent its formation, thus maintaining the patency of the lymphatics and capillaries and facilitating the dissemination of the organisms. The production of fibrinolytic or antifibrinogenic substances and the invasiveness of a given strain of Streptococcus are correlative. Both substances are relatively thermostable. Fibrinolysin is destroyed if held at 100 C. for one hour. The antifibrinogenic substance is weakened but is not destroyed under the same conditions. There is evidence that both substances are antigenic, and that they exhibit some degree of type specificity. The rôle of fibrinolysin and that of the antifibrinogenic factor in the invasion of the tissues by streptococci are discussed. FROM THE AUTHORS' SUMMARY.

DISSOCIATION OF STREPTOCOCCI FROM ACUTE RHEUMATIC FEVER. K. M. HOWELL and E. P. BURTON, J. Infect. Dis. **55**:79, 1934.

Four strains of streptococci freshly isolated by blood cultures from patients with acute rheumatic fever remained virulent and smooth for eight months in spite of efforts to incite dissociation by chemical and physical means and by inoculation into animals. Elements of dissociation in the strains are suggested by pleomorphism and by occasional S-R colonies. The experiments with animals suggest little possibility of changing a smooth virulent strain to a rough avirulent strain in vivo. Accepting the definition that dissociation is a permanent change that takes place in a bacterium and is then transmitted to subsequent generations, we have so far been unable to dissociate the four strains of streptococci obtained by blood culture from patients with acute rheumatic fever.

FROM THE AUTHORS' CONCLUSIONS.

DIPHTHERIA BACILLI: CULTURAL AND TOXIGENIC CHARACTERISTICS. L. W. SMITH, M. E. SANO and J. J. JAREMA, J. Infect. Dis. **55**:105, 1934.

The incidence of toxic cultures in carriers of different types has been presented, scarlet fever carriers having the greatest percentage. The persistence of toxicity in carrier strains and the uselessness of repeated tests in these cases is commented on. No relation between the formation of a pellicle and toxicity has been found. No relationship between toxicity and hemolysis has been observed. Of thirty different strains none was found to be soluble in bile. The morphology of the bacillus and the toxicity did not seem to show more than a suggestive relationship. The presence of a coccoid form in Berkefeld "N" filtrates after incubation was observed. Histologic examination of the tissues of guinea-pigs utilized in this study showed a fairly uniform tendency to lymphoid hyperplasia and germinal center lymphoid necrosis in the animals given the toxic strains; relatively no changes were observed in those given the nontoxic strains.

FROM THE AUTHORS' SUMMARY.

A Biologic Classification of the Bacillus of Rhinoscleroma. M. C. Morris and L. A. Julianelle, J. Infect. Dis. **55**:150, 1934.

A study of the biologic and immunologic reactions of ten strains of the bacillus of rhinoscleroma has been made. All these strains exhibited an inability to form indole or to liquefy gelatin, but all were able to reduce nitrates. The Voges-Proskauer and methyl red tests were found to be of no value for diagnosis or classification. The fermentation reactions were characterized by absence of gas. The sugars fermented were dextrose, maltose and mannitol, and in three instances there was a delayed formation of acid in sucrose. Lactose was not fermented, and litmus milk showed no gross changes. None of the strains was virulent for white mice. The agglutination reactions demonstrated the serologic unity of the strains of the bacillus of rhinoscleroma and its antigenic similarity to type C of Friedländer's bacillus. By agglutinin adsorption it was shown that both organisms have identical serologic specificity.

From the Authors' Summary.

Psittacosis Among the Personnel of the Hygienic Laboratory. G. W. McCoy, J. Infect. Dis. **55**:156, 1934.

The epidemiological features in association with eleven cases of psittacosis occurring among the personnel of a research laboratory are described. Two of the eleven persons infected were in direct contact with infected birds. While the ultimate source of the infection of the other nine persons probably was infected birds, the means of transmission of the disease were not determined. It seems to be established that person-to-person infection did not occur.

From the Author's Summary.

Institutional and Occupational Undulant Fever in Colorado. I. C. Hall and R. Learmonth, J. Infect. Dis. **55**:184, 1934.

Whenever possible, tests on both the blood serum and the milk serum should be made to detect agglutinins for Bacterium melitensis (or Bacterium abortus) in dairy cattle. Tests of blood serum are superior to tests of milk serum. Undulant fever is transmitted most commonly, first, through handling infected meat in slaughter houses and, second, through drinking raw milk from infected dairy cattle. All the milk should be pasteurized to protect the inmates of institutions against contracting undulant fever from cows harboring abortion disease. Meat inspectors run a much greater risk of contracting this fever than do employees in hog cholera serum plants.

From the Authors' Summary.

Examination of Children with Infection of the Upper Respiratory Tract for Bacillus Pertussis by the Cough Droplet Method. H. L. Wilcox, J. Infect. Dis. **55**:199, 1934.

The inability to isolate the pertussis bacillus by the cough droplet method in patients with infections of the upper respiratory tract other than whooping cough, the negative results obtained by other investigators from cultures of material from the nasopharynx and larynx of persons not in contact with whooping cough and the negative pulmonary and laryngeal cultures made postmortem on children who died from various other causes add to the view that the pertussis bacillus is found only in persons who have or who have had whooping cough and in those who have been in contact with the disease.

From the Author's Summary.

Differentiation of Streptococcus Epidemicus. I. Pilot, J. Infect. Dis. **55**:228, 1934.

Mucoid encapsulated organisms of the Streptococcus-Pneumococcus group can be differentiated into Streptococcus epidemicus, Streptococcus Mathersi and Pneumococcus mucosus. These strains may be mucoid variants of Streptococcus haemo-

lyticus, Streptococcus viridans and Pneumococcus. Str. epidemicus appears to be the only organism identified with milk-borne epidemics of septic sore throat; Mathers' coccus appears during epidemic or pandemic influenza. Mucoid strains of the Streptococcus group apparently are important factors in the genesis of epidemic diseases.

FROM THE AUTHOR'S SUMMARY.

A SURVEY OF WORKERS IN PACKING PLANTS FOR EVIDENCE OF BRUCELLA INFECTION. L. HEATHMAN, J. Infect. Dis. **55**:243, 1934.

While experience has shown that the agglutination test is a valuable diagnostic aid to the clinician, the data presented point clearly to the necessity for interpreting the laboratory findings in the light of a full history and the clinical signs and symptoms. The findings in this study, together with the observations on the incidence of the allergic state in well persons without a history of undulant fever or known exposure to brucella infection, cited in this paper, lead to the conclusion that the intradermal test is of little value as a diagnostic aid. In dealing with persons exposed to brucella infection, the greatest care must be exercised in the interpretation of both the positive agglutination and the positive intradermal test.

PARATYPHOID B IN WESTERN NORWAY. T. M. VOGELSANG, J. Infect. Dis. **55**:276, 1934.

Investigation of 208 strains of Bacillus paratyphosus B from 100 patients with paratyphoid fever, type B, has yielded the following results: B. paratyphosus B occurs in different cultural forms. During the illness and the stage of convalescence the S form alone is found, while the R form, mixed as a rule with the S form, is observed in persons who have been excreting the organisms over a comparatively long period. B. paratyphosus B constitutes a special type among the bacteria of the Salmonella group, with definite cultural and biologic qualities, viz., "slime wall" formation at room temperature; formation of papillae on raffinose agar; formation of hydrogen sulphide in lead acetate agar; a negative Bitter reaction; a negative Pesch-Maschke reaction, and decolorization of neutral red agar. The dextrotartrate test is valuable in the differentiation of B. paratyphosus B (which is "tartrate-negative") from the closely related humanopathogenic "tartrate-positive" types of Salmonella. B. paratyphosus B ferments the same sugars and polyvalent alcohols as the closely related humanopathogenic types of Salmonella, with formation of acid and gas. According to the time taken to ferment inosite and rhamnose, B. paratyphosus B can be divided into several types, which appear to be so constant in their occurrence in the individual patient and in any one epidemic as to be of practical significance in epidemiological inquiries. In its serologic manifestations B. paratyphosus B constitutes a definite diphasic type of Salmonella. It has both a heat-stable O antigen and a heat-labile nonspecific H antigen in common with several other types of Salmonella, while none of the other known types contains the heat-labile specific H antigen peculiar to it. The change of the S form to the R form is accompanied by an alteration in the O antigen, while the H antigens remain unaltered. B. paratyphosus B gives rise to a typhoidal clinical picture which cannot be differentiated by the clinical manifestations alone from typhoid. In a few patients the illness had an acute onset but gradually passed into a condition resembling typhoid. In no instance did the illness throughout its entire course behave like acute gastro-enteritis. In most cases the intestinal ulceration involves mainly the colon (colotyphoid). Broadly speaking, each of the two diseases, paratyphoid B and typhoid, has its own area of distribution in western Norway. While both diseases previously showed a wide dissemination, it has been possible during the last ten years to produce a more or less regular decline in their incidence. The sources and paths of infection are of the same nature in both diseases. Chronic carriers are the source of greatest moment, and under the present conditions milk furnishes the main path of infection. The same preventive regulations have been shown to be effective against both diseases. Disease among animals is not observed in association with paratyphoid B in man. Paratyphoid B

is transmitted directly or indirectly from person to person and appears to be as specific a disease in man as typhoid. Other primary sources of infection, the subject of scientific argument, have not been established with certainty.

FROM THE AUTHOR'S SUMMARY.

RELATIONSHIP OF THE MORPHOLOGY OF THE DIPHTHERIA BACILLUS TO ITS VIRULENCE. J. J. JAREMA and L. W. SMITH, J. Infect. Dis. **55**:306, 1934.

During the routine examination of 592 nose and throat cultures for virulent diphtheria bacilli, observations were made which show a decided relationship between morphology and virulence in these organisms: A greater percentage of virulence was shown by mixed cultures than by cultures of pure types. Cultures that were of the BT type, that is, bacilli which showed a tendency to bulge at one or both poles or anywhere along the body, were always found by inoculation into animals to be virulent. Fifty-nine per cent of the virulent strains were of the BT type. Elimination of the inoculation of the BT type into animals would result in a saving of time and material. A clinical correlation was found between the presence of the BT type and the severity of the disease. Repeated virulence tests on cultures from diphtheria carriers and from patients with clinical diphtheria showed a definite relationship between the morphology and the virulence of the diphtheria organism.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL SUMATRAN MITE FEVER IN GUINEA-PIGS. W. KOUWENAAR and J. W. WOLFF, J. Infect. Dis. **55**:315, 1934.

Monkeys, rabbits and guinea-pigs were inoculated with material containing the virus of Sumatran mite fever. A high percentage of the monkeys reacted to intradermal inoculation with a primary papule, swelling of the lymphatic glands, fever, leukopenia and relative lymphocytosis, and the blood gave a positive Weil-Felix reaction with Bacillus proteus X Kingsbury. In rabbits, after intratesticular infection a specific orchitis developed; after intra-ocular infection, a specific keratitis and iridocyclitis occurred occasionally in guinea-pigs; after intraperitoneal or intratesticular infection, a disease developed characterized by loss of weight, occasional fever, high infiltration of the omentum and parietal peritoneum by histiocytes, hemorrhagic edema of the polar fat body of the testicle, interstitial infiltration of the testicle, tunica vaginalis and cremasteric muscle, swelling of the suprarenal and lymphatic glands, transitory swelling of the spleen and sometimes infiltrations of the brain. The disease could be transmitted from man to monkeys, rabbits and guinea-pigs, and from each of these animals to the others. Rickettsiae were found in monkeys, rabbits and guinea-pigs. Mite fever seems to differ from tsutsugamushi disease, *fièvre boutonneuse* and South African tick fever. Mite fever is closely related to, or is perhaps identical with, the scrub variety of tropical typhus.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL FUSO-SPIROCHAETAL INFECTION IN GUINEA PIGS. H. O. PROSKE, Pub. Health Rep. **49**:1212, 1934.

Fusospirochetal lesions comparable with those occurring in man may be caused by the symbiotic action of Treponema microdentium or mucosum, Bacillus fusiformis serologic type I, subtype 2, or type II (Varney), an anaerobic anhemolytic streptococcus and Vibrio viridans. Original cultures were taken from miners with silicosis who had pulmonary abscess and chronic bronchiectasis. Treponema macrodentium, Treponema buccale, Spirillum sputigenum and a larger fusiform bacillus growing together with a spirochete resembling Treponema Vincenti take no part in the symbiotic action. The anaerobic streptococcus and the vibrio, by virtue of their mild but definite pathogenic properties, appear to render the tissues susceptible to the destructive action of the other types of organisms. This experimental study furnishes evidence in support of a conclusion of D. T. Smith (*J. Infect. Dis.* **46**:

303, 1930) that pulmonary lesions may be caused by a symbiosis of a spirochete, a fusiform bacillus, a vibrio and a coccus. Further investigations are indicated as to whether any pathogenic organisms (anaerobic or aerobic) of the upper respiratory tract may replace one or the other of the members of the harmful symbiotic group just described.

FROM THE AUTHOR'S SUMMARY.

PSITTACOSIS IN THE POCKET GOPHER. R. D. LILLE, Pub. Health Rep. **49**:1419, 1934.

Gophers inoculated with the virus of psittacosis, to which they are quite susceptible, present a fairly consistent and characteristic pathologic picture: in the liver, focal fibrinocaseous necrosis, isolated coagulated cells, occasional small coagulation necroses and slight swelling of Kupffer cells; in the spleen, widespread fibrinous thrombosis of the pulp, accompanied by karyorrhexis in the tissue cells, grading into caseous necrosis; in the lungs of some animals, congestion, hemorrhage and edema; in the heart muscle and kidneys, cloudy swelling.

FROM THE AUTHOR'S SUMMARY.

THE DEVELOPMENTAL FORMS OF PSITTACOSIS VIRUS. S. P. BEDSON and J. O. W. BLAND, Brit. J. Exper. Path. **15**:243, 1934.

The apparently homogenous masses seen in the early stages of the multiplication of the virus of psittacosis are particulate. FROM THE AUTHORS' SUMMARY.

VARIATION IN THE PNEUMOCOCCUS. M. H. DAWSON, J. Path. & Bact. **39**:323, 1934.

A new and distinct variant of Pneumococcus is described. The place of the new variant in the general phenomenon of bacterial variation is indicated. A change in the currently accepted nomenclature of variant forms of Pneumococcus is suggested to conform with that now employed to describe corresponding variant forms of other bacterial species. In accordance with this change it is proposed that the three chief variants of Pneumococcus shall be designated by the terms M (mucoid), S (smooth) and R (rough). Various stages in the S → R and R → S variations (new terminology) of Pneumococcus are described. Morphologic evidence is presented which suggests that these variations may be cyclic.

FROM THE AUTHOR'S SUMMARY.

THE PORTAL OF ENTRY OF BACTERIA AND THE PRODUCTION OF INTESTINAL INFECTION. F. H. TEALE, J. Path. & Bact. **39**:391, 1934.

The buccopharyngeal mucous membrane is permeable to bacteria without previous injury. The normal gastric juice is germicidal in proportion to the percentage of the physiologically active hydrochloric acid. The normal intestinal mucosa is practically impermeable to bacteria along its whole length. The mucous membrane of the whole length of the alimentary canal acts as a channel by which bacteria are excreted from the body. Intestinal disease may occur as the result of oral infection through the buccopharyngeal mucosa, extension to the regional lymphatic glands and spread by the blood stream to the intestinal mucosa. In some cases the infection may be primarily enteral, something having occurred which altered the permeability of the epithelium and glands so that they allow bacteria which have escaped the germicidal activity of the gastric juice to invade the mucosa. Enterotropism is really only a clinical manifestation depending on the resistance of the intestinal mucosa to the bacterium. All bacteria are enterotropic in that they are passed from the tissues into the lumen of the intestine, but the occurrence of intestinal symptoms depends on the virulence of the bacterium relative to the resistance of local tissue. The self-sterilization of the alimentary tract is not due to any germicidal secretion by the intestinal mucosa but is due simply to the competitive action of the normal intestinal flora.

FROM THE AUTHOR'S CONCLUSIONS.

THE PLEUROPNEUMONIA AND AGALACTIA COLONY. E. KLIENEBERGER, J. Path. & Bact. **39**:409, 1934.

By the aid of a modified agar-fixation method it has been possible to unravel the structure of the pleuropneumonia and agalactia colony at all stages of growth. Study of the fixed and stained colonies reveals a mode of development and a resultant structure agreeing in all essential features with those postulated by Ledingham in his study of impression preparations. The life cycle of these organisms appears to be essentially simple, despite the obvious polymorphism of the constituent elements. Further search for possibly saprophytic homologs must be made before attempting to assign to them generic rank in the family of Actinomycetaceae in which Ledingham proposes to enrol them. In a study of the influence of varying conditions of growth on morphologic structure it has been found that lithium salts incorporated in the medium cause remarkable alterations in the size and shape of the pleuropneumonia and agalactia "bodies" not unlike the changes incurred by bacteria under similar influences.

FROM THE AUTHOR'S SUMMARY.

HAEMOLYTIC STREPTOCOCCI FROM THE VAGINA OF FEBRILE AND AFEBRILE PARTURIENT WOMEN. R. HARE and L. COLEBROOK, J. Path. & Bact. **39**:429, 1934.

Only a minority of the strains of hemolytic streptococci from the vagina of afebrile parturient women give the same biochemical reactions as those from patients with definite infections. The majority of the saprophytic strains are probably of the same type as that which causes a large proportion of cases of bovine mastitis. A proportion of mild puerperal infections are probably due to such bovine strains.

FROM THE AUTHORS' CONCLUSIONS.

TYPES OF CORYNEBACTERIUM DIPHTHERIAE. D. T. ROBINSON, J. Path. & Bact. **39**:551, 1934.

In stock subcultures typical strains of Corynebacterium diphtheriae in Manchester, England, showed marked stability, but by special in vitro methods it was possible to obtain variation in most of the type characters. In respect to gravis strains starch fermentation was not perfectly stable, but appeared to be more so than colony form. By agglutination there was no distinction between the "smooth" and "rough" colonies of gravis. Animal passage also revealed a high degree of type stability. One instance of apparent complete change of type by means of papilla formation was observed. Some atypical strains may show marked instability both in vivo and in vitro. The appearance of mixed types in primary cultures and in cultures from convalescents in the hospital is due, in the vast majority of cases, to cross-infection and not to variation. In areas where the disease is severe or where an epidemic strain is prevalent the classification into gravis, mitis and "intermediate" types is straightforward. Atypical strains and difficulties in classification are much more frequent in areas where the disease is mild and where none of the types has an epidemic distribution. Reversal of the reaction in broth and hemolysis are not valuable as criteria for the classification of gravis and mitis strains; but "intermediate" strains apparently never hemolyze and never cause reversal of the reaction in broth.

FROM THE AUTHOR'S SUMMARY.

CORYNEBACTERIUM OVIS, CORYNEBACTERIUM DIPHTHERIAE AND CERTAIN DIPHTHEROID STRAINS. G. F. PETRIE and D. MCCLEAN, J. Path. & Bact. **39**:635, 1934.

There is no relationship between the specific toxins that are present in filtrates of both cultures of C. ovis and C. diphtheriae. An examination of the toxin-antitoxin relations of C. diphtheriae, Mair's aberrant strain of C. diphtheriae, the group of aberrant diphtheroid strains described by Barratt and C. ovis has shown that these strains possess characters which link them together. The strain discovered by Mair occupies a key position in the group because it has an affinity not only to the typical C. diphtheriae but to C. ovis and to the aberrant diphtheroid strains of Barratt.

FROM THE AUTHORS' SUMMARY.

CARBOHYDRATE AND NUCLEOPROTEIN FRACTIONS OF BRUCELLA. L. E. TOPPING, J. Path. & Bact. **39**:665, 1934.

The results recorded indicate that Brucella abortus contains, in addition to a nontype-specific nucleoprotein fraction similar to that described by Huddleson (1933), a carbohydrate which precipitates with Br. abortus and B. melitensis antiserums.

Immunology

HETEROPHILE ANTIGEN IN VARIOUS BACTERIAL SPECIES. MARY SHAW SHORB and G. HOWARD BAILEY, Am. J. Hyg. **19**:148, 1934.

Fourteen bacterial species were proved to contain heterophilic (Forssman) antigen by their stimulation of the development of antisheep hemolysin in rabbits and by absorption experiments. The highest titers were obtained by Neisseria catarrhalis and Streptococcus viridans. The heterophilic nature of the antigen in the bacteria and of the antibodies in the immune serums was determined by all known methods. Only three of the bacterial species produced antiserums which agglutinated sheep cells, while all produced antiserums that hemolyzed them. Human red blood cells of group A were agglutinated by all but one of the bacterial heterophilic immune serums, while none of the serums was able to hemolyze human blood corpuscles. Similar variations were observed with regard to the ability of the antiserums to produce toxic cutaneous reactions in guinea-pigs and with regard to the ability of the bacteria to absorb the antibodies from the different antiserums. The antigenic properties of alcoholic extracts of the bacteria were lower than those of the intact bacteria or of their aqueous solutions. According to Shorb and Bailey, the presence of heterophilic antigens in such widely distributed bacterial species as N. catarrhalis, Diplococcus pneumoniae, Clostridium Welchii and Alcaligines faecalis may explain the origin of normal antisheep hemolysin. Many bacterial species, among them important pathogens, were found not to contain heterophilic antigen.

I. DAVIDSOHN.

THE TRYPANOCIDAL ACTION OF NORMAL HUMAN SERUM. J. T. CULBERTSON and P. S. STRONG, Am. J. Hyg. **21**:1, 1935.

Because the substance in fresh human serum responsible for the trypanocidal effect is relatively thermostable, is able to pass through a Berkefeld filter, and is absorbable from the serum by trypanosomes as well as by certain species of bacteria it is postulated that the substance is a relatively nonspecific antibody, perhaps similar to the substance responsible for bactericidal activity.

THE TRYPANOCIDAL POWER OF NORMAL HUMAN SERUM. B. J. HANDLER, Am. J. Hyg. **21**:18, 1935.

The results reported may be taken to indicate that the trypanocidal agent in normal human serum is capable of producing an equivalent antibody, or else that its function is closely associated with some antigenic factor. When sufficient antiserum prepared against unheated human serum is added to normal human serum in vitro, neither the supernatant fluid nor the precipitate displays any trypanocidal activity. However, when an antiserum prepared against heated human serum is used under similar conditions, the trypanocidal power of the supernatant fluid is not diminished. Similarly, an antagonistic effect in vivo could be elicited only with antiserum obtained by immunization with unheated human serum. The inability of earlier observers to demonstrate that antihuman serum has an inhibitory effect on the trypanocidal principle of normal human serum is probably best explained on the basis of improper proportions or a lack of potency.

THE ANTIBODY RESPONSE OF RABBITS TO TYPE I PNEUMOCOCCUS VACCINES. L. A. BARNES and B. WHITE, Am. J. Hyg. **21**:35, 1935.

The evidence taken as a whole suggests that the following factors are involved in producing in rabbits highly protective type I antipneumococcic serum: (*a*) preliminary stimulations with gradually increasing amounts of vaccine until the optimum amounts are reached; (*b*) after the "holding dosages" are reached, the alternation of relatively long rest periods with repeated secondary stimulations, and (*c*) the allowance of a sufficient length of time. Similar procedures are being applied in the routine immunization of horses for the production of therapeutic antipneumococcic serums.

FROM THE AUTHORS' SUMMARY.

ARTIFICIAL IMMUNIZATION OF RATS AGAINST TRICHINELLA SPIRALIS. O. R. MCCOY, Am. J. M. Sc. **21**:200, 1935.

The majority of rats given six intraperitoneal injections of living, heat-killed or dried and powdered larvae at five day intervals developed some degree of immunity against a subsequent light infection with Trichinella spiralis. The degree of immunity varied from none to practically complete. The living larvae were usually more effective in establishing immunity than either the heat-killed or the dried and powdered larvae. Artificially immunized rats showed little or no resistance to the initial development of adult worms in the intestine, but the worms were lost more rapidly than in control animals. This would result in a smaller amount of muscle invasion in the immunized rats. The immune state produced by the injections is apparently of the same general nature as that brought about by infection; in each instance the mechanism is directed against the intestinal stages of the parasite. The former immunity, however, is not nearly so potent as the latter and is much more easily broken down by large doses of larvae.

FROM THE AUTHOR'S SUMMARY.

THE TIME INTERVAL BETWEEN PRIMARY INFECTION AND SUPERINFECTION AS A FACTOR IN IMMUNITY TO TUBERCULOSIS. HENRY SEWALL, EUGENE DE SAVITSCH and CHARLES P. BUTLER, Am. Rev. Tuberc. **29**:373, 1934.

The results of studies in guinea-pigs furnish evidence that superinfection (a term adopted as less subject to criticism than that of reinfection) has the power, under certain circumstances, not only to increase fibrosis and aid in the segregation of foci of infection, but also to stimulate actively the resistance to the implantation of fresh bacilli, if not, indeed, to cause the absorption of foci of disease already formed. The results point to a single variable as of paramount importance in achieving resistance (immunity within the host), namely, the interval of time between infection and superinfection. The data suggest certain steps in the development of immunity. Among the factors concerned is a specific hypersensitiveness of the body tissues toward the antigen, which is foreign and presumably injurious to the invaded host. The evidence stresses the importance of the time element in the development of tissue immunity. At a certain period after infection the violence of the local reaction to reinfection begins to diminish steadily; on the other hand, the general stability of the reacting host—his power of adaptation and restoration, that is, immunity—at the same time increases. The local inflammation and other manifestations caused by superinfection at fifty-three days denote allergy. At this period the whole body probably shares the allergic state. On withholding superinfection for stated periods, allergy diminishes but immunity increases. Far from stigmatizing allergy as indifferent or antagonistic to the development of immunity, Sewall, de Savitsch and Butler take the view that it represents crude vital energy specifically excited and capable of adaptation to the protection of the host, whose tissues are trained by stimulation of the antigen which first aroused them. Sewall (*Nat. Tuberc. A. Tr.* **28**:84, 1932) classified the conditions of combat between the host and the pathogen under three heads: (1) a host-defensive mechanism so perfect that the invader is destroyed without disturbance

—perfect immunity; (2) a virulence of the pathogen so overwhelming that the host quickly succumbs—defenseless susceptibility; (3) the two contestants approximately equal, so that the outcome of the struggle depends on the relative allergic resources of the combatants, the allergic reaction becoming less acute in proportion as one or the other prevails.

H. J. CORPER.

IMMUNIZATION OF THE UPPER RESPIRATORY TRACT. T. E. WALSH and P. R. CANNON, Arch. Otolaryng. **20**:820, 1934.

Repeated intranasal instillations of vaccines prepared from Bacterium paratyphosum B or Bacterium typhosum caused the development of specific agglutinins in the various organs and in the blood of the treated animal. Simultaneous titration of different tissues of a perfused animal revealed that the agglutinin content of the nasal tissues was usually higher than that of any other organ tested, but lower than that of the blood serum. Agglutinins in the nasal tissues were demonstrable in fairly high dilution only after intranasal instillation of the vaccine for at least six days, the highest titers being in animals treated daily for from nine to thirteen days with extraction and titration of the tissues from five to seven days after the last vaccination. The repeated intranasal application of these vaccines caused structural changes in the subepithelial tissues, with an accumulation of leukocytes, macrophages and mononuclear cells, and hyperplasia of the lymphoid tissues. The agglutinin content of the nasal tissues in a few instances was higher than that of the blood serum or of other tissues of the same animal, suggesting that the antibody formed locally in the region of vaccination. Nonspecific stimulation of the nasal tissues of rabbits immunized subcutaneously and possessed of a high titer of the agglutinins of the blood serum did not lead to as high titers of the agglutinins of the extracted nasal tissues as was usually the case after intranasal vaccination. Living bacteria instilled into the nostrils did not enter the blood stream in detectable numbers within an hour, thus demonstrating the barrier action of nasal and nasopharyngeal epithelium. A solution of trypan blue instilled into the nostrils entered the lungs directly by way of the trachea. The experiments support the notion that local intranasal vaccination may lead to local concentration of specific agglutinins in the nasal tissues and mobilization of leukocytes and macrophages in the subepithelial tissues of the upper respiratory tract. They also furnish evidence for the view that these agglutinins are, at least in part, formed locally. Complete proof of this point is still lacking. The conclusion is drawn that local immunization by mobilizing macrophages and by favoring the formation or concentration of specific antibody in the region of vaccination should enhance the resistance of such tissues against similar living bacteria.

FROM THE AUTHORS' SUMMARY.

IS THERE A SCARLET FEVER TOXOID? G. F. DICK and G. H. DICK, J. A. M. A. **103**:1362, 1934.

Scarlet fever toxin is partially but not completely detoxified by treatment with solutions of formaldehyde up to 1 per cent. The presence of unaltered toxin in the formaldehydized preparation is sufficient to account for the immunity obtained. No evidence now available justifies the assumption that there is a scarlet fever toxoid analogous to diphtheria toxoid. Alum precipitates diphtheria toxin, and the toxin may be demonstrated in the precipitate; but the redissolved alum precipitate from scarlet fever toxin showed no evidence of the presence of toxin. The rabbit is not a suitable subject for standardization of scarlet fever toxin. Since the detoxified portion of scarlet fever toxin that has been treated with dilute solution of formaldehyde is not antigenic, it is inferior to unmodified toxin as an immunizing agent because of the unnecessary amount of useless foreign protein which it contains.

FROM THE AUTHORS' SUMMARY.

ANTIBODY RESPONSES IN INFECTIOUS MONONUCLEOSIS. ALAN BERNSTEIN, J. Clin. Investigation **13**:419, 1934.

Bernstein tested the serums of 300 patients for the presence of agglutinins for sheep red corpuscles. Among the patients were: (*a*) 29 with different clinical conditions the clinical features of which were similar to those of infectious mononucleosis; (*b*) patients with conditions which are associated with bacterial agglutination reactions (typhoid and paratyphoid fever, dysentery, etc.); (*c*) patients with various blood dyscrasias. Over 95 per cent had a titer of 1:8 or less, and none a titer higher than 1:16 (with Davidsohn's first method of agglutination of sheep red corpuscles). In 18 patients who had been treated with horse serum, the titer was regularly elevated (the highest was 1:512). Of 15 patients with clinical features of infectious mononucleosis, 13 had moderately to markedly elevated titers of agglutinins for sheep cells (varying from 1:32 to 1:4,096); in 2 patients the titers were normal. In some of the cases, the increase of the antibodies preceded the appearance of abnormal blood findings (in 1 case by four days). Two cases with unusual features are described; in one of them there was a high titer of agglutinins for sheep cells and, in addition, there was an elevation of the titer of agglutinins for various bacteria of the typhoid and paratyphoid groups. The patient had received typhoid vaccine for over a year previous to the last illness. The other patient had the findings of a purpura and a marked elevation of the titer of heterophilic antibodies. Bernstein considers the conditions observed in both cases as being due to infectious mononucleosis, possibly in association with other disorders. In two cases a transient positive Wassermann reaction was observed.

I. DAVIDSOHN.

THE DIAGNOSTIC IMPORTANCE OF THE HETEROPHILE ANTIBODY TEST IN LEUKEMIA. ALAN BERNSTEIN, J. Clin. Investigation **13**:677, 1934.

Bernstein found that in twenty of twenty-one patients with leukemia (lymphatic, myelogenic and monocytic) the titer of heterophilic antibodies (agglutinins for sheep red blood cells) was uniformly lower than in most normal persons and in patients suffering from diseases which resembled leukemia clinically. The range of titers in the serum of leukemic patients was not higher than 1:4 (with use of the technic of the reviewer), while in the controls it varied from 1:1 to 1:16. Injection of horse serum failed to stimulate an elevation of heterophilic antibodies in a patient with leukemia and in one with leukosarcoma. The diagnostic significance of the findings is emphasized.

I. DAVIDSOHN.

THE FATE OF AVIRULENT STREPTOCOCCI INJECTED INTO THE SKIN OF NORMAL AND SENSITIZED RABBITS. D. M. ANGEVINE, J. Exper. Med. **60**:269, 1934.

Histologic examination showed that the inflammatory reaction following the injection of hemolytic streptococci into rabbits sensitized to this organism began sooner than in the normal animal; edema was more extensive, and both polymorphonuclear leukocytes and large mononuclear cells appeared sooner. The lesion of a sensitized animal was more sharply circumscribed, and there was necrosis of tissue, seldom seen in the normal animal. In sensitized animals local injury, with necrosis, favors the multiplication of relatively avirulent streptococci at the site of entry and explains their survival at a time when they have disappeared in the controls. In association with greater local injury and a more intense inflammatory reaction in the sensitized animal as compared with the normal, streptococci are fixed at their site of entry; they pass to adjacent lymph nodes in much smaller numbers and fail to reach the blood and internal organs.

FROM THE AUTHOR'S SUMMARY.

THE MATERNAL TRANSMISSION OF VACCINIAL IMMUNITY IN SWINE. J. B. NELSON, J. Exper. Med. **60**:287, 1934.

The protective substances produced by vaccinia virus in swine were transmitted repeatedly to the young by way of the colostrum of the sow. In two instances immunity acquired by suckling was demonstrable in the young of six successive

farrowings, which numbered thirty-seven and fifty-seven pigs, respectively. The immunity acquired by suckling began to decline during the second month and was practically negligible by the end of the third month. Vaccinia virus introduced cutaneously during the first few days of life in the passively protected pigs exerted little or no immunizing effect. FROM THE AUTHOR'S SUMMARY.

THE EFFECT OF ANTECEDENT INFECTION AND IMMUNIZATION WITH STREPTOCOCCI UPON THE REACTIVITY OF RABBITS TO HORSE SERUM. M. P. SCHULTZ and H. F. SWIFT, J. Exper. Med. **60**:323, 1934.

The cutaneous responses of rabbits to small doses of horse serum given intracutaneously are described. After an original injection of 0.1 cc. a secondary reaction often occurs about the ninth day, and tests at three day intervals with 0.001 cc. indicate that general cutaneous hypersensitivity is established at this time. Circulating precipitins for horse serum appear later. As the degree of sensitivity increases, the lesions resulting from test doses reach a maximum development more quickly. The reactivity of rabbits to horse serum is greatly increased by antecedent sensitization of the animals with repeated small intracutaneous inoculations of indifferent streptococci or by immunization with large intravenous injections of either indifferent or hemolytic streptococci. Doses of indifferent streptococci precisely comparable to those producing greatly enhanced reactivity when given intracutaneously increase reactivity to horse serum irregularly and to a slight degree when injected intravenously. Increases in reactivity (allergic irritability) are made evident by the occurrence of larger skin lesions at the sites of the primary injections of horse serum, by an earlier development of more distinct secondary reactions in a higher percentage of animals and by a more rapid appearance of skin sensitivity to the small test doses, which may be first evidenced by delayed reactions at these injection sites. Accompanying these evidences of increased reactivity there is an early appearance of blood serum precipitins in high titer. There was no evidence of residual inflammation in any of the animals at the time reactivity to horse serum was tested. No attempt was made to determine the duration of this altered reactive capacity. It has been encountered in tests begun from eight to fourteen days after the last preliminary inoculation. It is suggested that the increased reaction described is brought about by a persisting alteration in the functional activity of the reticulo-endothelial system.

FROM THE AUTHORS' SUMMARY.

THE INFLUENCE OF SEXUAL MATURITY UPON THE REACTIVITY OF RABBITS TO HORSE SERUM. M. P. SCHULTZ, J. Exper. Med. **60**:339, 1934.

Normal rabbits in the course of their development, after infancy, vary in their responses to minute doses of horse serum given intracutaneously. There is increased reactivity in males as they mature, beginning, in the stock employed in these experiments, at about the age of 13 weeks, when a weight of 1,700 Gm. has been attained. The reactivity of normal females remains at a constant level, and the increase demonstrated in males does not take place in the females. The divergence in the degree of reactivity of males and females, beginning with the establishment of estrus, indicates that factors associated with sexual maturity in females are responsible for their low reactivity. The suppression of estrus by operative removal of the ovaries resulted in an increase of reactivity which, however, in the experiments reported here was probably not great enough to account entirely for the difference in the reactivity of mature males and females.

FROM THE AUTHOR'S SUMMARY.

ANTIBODY FORMATION AFTER EXTIRPATION OF THE ANTIGEN-DEPOT. P. R. CANNON and K. L. BURT, J. Immunol. **27**:173, 1934.

The extirpation of the antigen depot within from three seconds to ten minutes after the intradermal injection of a heavy suspension of living staphylococci or bacilli prodigiosi does not necessarily prevent their entrance into the blood stream

and their later deposition in the liver and spleen. Postulation of a new mechanism for the production of antibody after removal of the antigen depot is unnecessary, at least until proof is available that antibody formation may occur independently of the escape of antigen from the original depot.

FROM THE AUTHORS' SUMMARY.

DIFFERENT TOXINS PRODUCED BY SCARLATINAL STREPTOCOCCI. S. B. HOOKER and E. M. FOLLENSBY, J. Immunol. **27**:177, 1934.

Numerous reliably observed discrepancies in the hypothesis that the mechanism of scarlet fever involves a single toxin are readily explained by assuming that multiple antigenic toxins exist. This report demonstrates the existence of two such toxins, A and B, whose qualitative distinctiveness is evidenced both by immunologic and chemical criteria. These include specific antigenicity, neutralizability and erythrogenic activity and the effects of dialysis, adsorbents, precipitants and enzymic digestion. Other erythrogenic streptococcus toxins undoubtedly exist. A single toxigenic strain may procure A or B or both or neither.

FROM THE AUTHORS' SUMMARY.

SERUM REACTIONS IN RHEUMATOID ARTHRITIS. M. H. DAWSON, M. OLMSTEAD and E. L. JOST, J. Immunol. **27**:355, 1934.

A comparative study of precipitins and agglutinins against Streptococcus haemolyticus has been made in the serums of seventy-one patients with rheumatoid arthritis and seventy-nine patients with other diseases. The results indicate that there is approximate, though not absolute, agreement of rheumatoid arthritis serums in their capacity to agglutinate strains of Str. haemolyticus and to precipitate various group-specific fractions of this organism. With certain exceptions, to which special reference is made, the control serums examined did not show the presence of either agglutinins or precipitins in significantly high dilutions. These findings offer suggestive evidence in favor of the hypothesis that rheumatoid arthritis is associated with infection by Str. haemolyticus.

FROM THE AUTHORS' SUMMARY.

IMMUNIZING SUBSTANCES IN PNEUMOCOCCI. L. D. FELTON, J. Immunol. **27**:379, 1934.

Pneumococci, both type I and type II, dried by application of acetone followed by desiccation in a vacuum, retain their antigenicity. The cell may be divided into acid-soluble and acid-insoluble constituents. The acid-soluble fraction possesses most of the immunizing activity of the cell; the immunity obtained by injecting this fraction into white mice is largely specific. The acid-insoluble fraction, perhaps containing some intact cells, also possesses a small amount of the immunizing substance and produces in white mice a heterologous immunity. With the method used in this study, at least 90 per cent of the immunizing substance in the acid-soluble fraction may be precipitated by ethyl alcohol or by acetone. The work reported here is limited to tests on white mice, and to antigenicity as produced by a single injection of the immunizing substance.

FROM THE AUTHOR'S SUMMARY.

Tumors

METASTATIC TUMORS OF THE HEART. E. M. BURKE, Am. J. Cancer **20**:33, 1934.

In a study of 327 autopsies on patients with known malignant growths, 14 cases of metastatic involvement of the cardiac muscle were found. These constituted approximately 4.3 per cent of the routine autopsies made in such cases at the State Institute for the Study of Malignant Disease. While the proportion seems somewhat higher than a review of the literature would indicate, it can probably be explained by the fact that this series includes only cases in which malignancy was definitely established and was definitely the cause of death.

AUTHOR'S SUMMARY.

RELATIONSHIP OF INTERNAL SECRETIONS TO MALIGNANT TUMORS. O. O. MEYER and C. MCTIERNAN, Am. J. Cancer **20**:96, 1934.

Thyroxine seems to inhibit tumor growth, but no other hormone has any demonstrable effect on tumor development, nor does removal of the glands of internal secretion which we studied prevent the usual rapid growth of sarcoma.

FROM THE AUTHORS' SUMMARY.

THE INFLUENCE OF LACTIC ACID AND SUGARS ON THE GROWTH OF TRANSPLANTED MOUSE SARCOMA 180. I. A. PARFENTJEV, V. D. SUNTZEFF and W. K. DEVRIENT, Am. J. Cancer **20**:117, 1934.

We may conclude that under the conditions of our experiments various preparations of lactic acid exert a relatively slight inhibiting effect on the growth of mouse sarcoma 180. This effect was especially noticeable after subcutaneous injections of solutions of ethyl lactate, lactyl-lactic acid and glyceromonolactate. The inhibiting effect was observed in experiments in which the weight of the treated animals was not unfavorably affected by these substances, a condition obtaining especially after the use of glyceromonolactate. This substance did not affect the weight of the mice unfavorably. However, it is probable that in the majority of the experiments the inhibiting effect of the lactic acid preparations on sarcoma 180 must be attributed in part to the unfavorable effect which these substances exerted on the metabolism of the animals. Injection of sugars (dextrose and arabinose) either exerted no inhibiting effect on the growth of sarcoma 180 or one less than that observed after administration of lactic preparations.

AUTHORS' CONCLUSIONS.

MYOBLASTOMA OF THE STRIATED MUSCLE. PAUL KLEMPERER, Am. J. Cancer **20**:324, 1934.

Six cases of myoblastoma of striated muscle are reported, and the literature is reviewed. About fifty cases have been recorded since the first description of this tumor seven years ago. The attainment of this high figure in such a comparatively short time indicates that myoblastoma of this nature is not uncommon. The chief localization is in the upper parts of the digestive and respiratory tracts. In the differential diagnosis xanthoma has chiefly to be considered.

FROM THE AUTHOR'S SUMMARY.

METASTATIC TUMORS OF THE ADRENALS. E. M. BURKE, Am. J. Cancer **20**:338, 1934.

A survey of 371 cases coming to autopsy showed that the suprarenal gland is a site of metastatic involvement in a relatively high percentage of malignant tumors. The majority of malignant tumors will metastasize to the suprarenal gland, this series showing primary lesions in various locations in the body. Certain types of tumor, however, metastasize more readily to this gland than do others. Either suprarenal gland may be involved, depending on the location of the original lesion. The suprarenal gland shows metastases in many cases in which there is no general dissemination. The medulla is the site of the metastatic neoplasm more frequently than the cortex.

FROM THE AUTHOR'S CONCLUSIONS.

A NEOPLASTIC DISEASE OF THE KIDNEY OF THE FROG, RANA PIPIENS. B. LUCKÉ, Am. J. Cancer **20**:352, 1934.

In the kidneys of 158 frogs of the species Rana pipiens there has been observed a neoplastic disease which manifests itself grossly as solitary or multiple ivory-white tumors. Histologically these are composed of atypical epithelial cells, grouped around spaces, thus giving a glandlike appearance to the growths. The tumors

are locally destructive and infiltrate the adjacent kidney. In the majority of the cases the histologic picture is that of adenocarcinoma. The tumors differ from human adenocarcinoma in their failure to metastasize. In a large proportion of the tumors prominent intranuclear inclusions are present, which may be regarded as presumptive evidence of the activity of a filtrable virus. It is therefore suggested that these tumors are either caused by such a virus or that a virus has invaded the new growths. A trematode larva and a myxosporidium were found in many of the tumor-bearing kidneys; these are not regarded as of etiologic importance. Experiments in transmission are as yet indecisive. Most of the cases of this disease have been seen in frogs from the state of Vermont and from the adjacent parts of Canada; the incidence has been on the average 2 per cent. Evidence pointing to more widespread distribution is presented. The literature on tumors of frogs is reviewed.

FROM THE AUTHOR'S SUMMARY.

MULTIPLE TUMORS IN TARRED AND RADIATED ANIMALS. M. C. REINHARD and A. A. THIBAUDEAU, Am. J. Cancer **20**:380, 1934.

The surprising fact that tumors developed relatively infrequently at the sites of painting leads one to consider the possibility that the action may not be strictly a local one, but a general response or intoxication due to the tarring.

RHABDOMYOSARCOMA OF THE SPERMATIC CORD. E. F. HIRSCH, Am. J. Cancer **20**:398, 1934.

A rhabdomyosarcoma of the right spermatic cord in a youth aged 16 years is described. The tumor consisted of long, fibrillar, spindle-shaped cells with cross-striations and of large multinucleated cells resembling segments of skeletal muscle fibers. These cells contained an abundance of glycogen granules.

FROM THE AUTHOR'S SUMMARY.

HAS THE CANCER CELL ANY DIFFERENTIAL CHARACTERISTICS? W. C. MACCARTY and E. HAUMEDER, Am. J. Cancer **20**:403, 1934.

This article discusses the results of comparative studies of the nucleolus and the nucleus in malignant and nonmalignant cells.

MULTIPLE PRIMARY CANCER. B. F. SCHREINER and W. H. WEHR, Am. J. Cancer **20**:418, 1934.

Primary multiple cancer occurred in 2.7 per cent of all cases of malignant growth observed. The most common primary multiple tumor is the basal cell epithelioma of the skin. The squamous cell or pearl-forming epithelioma of the skin is next in frequency. Combinations of basal cell and pearl cell epithelioma either in one person or in one specimen are not uncommon. Tumors of the mucous membrane of the oral cavity associated with malignant growth of the skin are third in frequency. Malignant epithelial tumors were associated with some variety of sarcoma in six cases. Primary bilateral cancer of the female breast was observed in fifteen cases and cancer of the breast associated with cancer of the female generative organs in eighteen cases. Leukemia was associated with cancer in four cases.

FROM THE AUTHORS' CONCLUSIONS.

METASTASIS OF MELANOMA BEFORE RECOGNITION OF PRIMARY GROWTH. S. SELIG, Am. J. Cancer **20**:594, 1934.

A case is described in which an apparently primary nonpigmented melanoma in the depth of the skin over the right heel metastasized in the groin four years before it was recognized. The tumor was radioresistant.

TRANSPLANTATION OF CARCINOMA DURING SKIN-GRAFTING. J. W. SPIES, F. E. ADAIR and M. C. JOBE, Am. J. Cancer **20**:606, 1934.

In a case of skin-grafting from the right thigh to cover a granulating surface after a mastectomy, mammary cancer appears to have been transferred to the area from which the grafts were taken.

AMYLASE IN MOUSE SARCOMA. F. H. SCHARLES, W. T. SALTER and P. D. ROBB, Am. J. Cancer **20**:613 and 625, 1934.

An enzyme found in aqueous extracts of mouse sarcoma 180 which is capable of splitting glycogen is described. Its activity is destroyed by heating at 100 C. for fifteen minutes or at 60 C. for one hour. The optimum temperature for its activity in vitro is 48-50 C., and the optimum p_H is about 6.2. The enzyme splits glycogen into several compounds, the ratio of whose reducing value to loss of glycogen is variable. The ratio depends both on the concentration of the extract used and on the time through which the reaction is allowed to continue. It is further shown that lactic acid is not produced directly from glycogen by crude tumor extract. When the glycogen concentration is varied, with constant concentration of the tumor extract or, conversely, when a variable concentration of tumor extract is used with a constant amount of glycogen, the loss of glycogen in a given time is a linear function of the logarithm of the concentration varied. On this fact is based a method, which is described, for measuring the activity of the enzyme.

The amylolytic activity of mouse sarcoma 180 has been studied in animals subjected to various chemical and physiologic conditions. Most of these produced no obvious variation in the amylolytic power of tumor tissue borne by the animals. The notable exceptions were injections of thyroxine and insulin, following which a definite change of enzymic activity could be demonstrated. No effect could be demonstrated from epinephrine.

FROM THE AUTHORS' SUMMARIES.

GENETIC STUDIES ON THE TRANSPLANTATION OF TUMORS. J. J. BITTNER, Am. J. Cancer **20**:834, 1934.

Rhythms of growth do not occur in transplanted tumors. The tumor cell does not become adapted. The tumor cell acquires no change in virulence. Hereditary factors determine the characteristics of both the host and the tumor cell. Animals of controlled genetic constitution are necessary for investigations based on tumor transplantation.

SACROCOCCYGEAL CHORDOMA IN CHILDREN. A. H. MONTGOMERY and I. J. WOLMAN, Am. J. Dis. Child. **46**:1263, 1933.

This article is based on the study of 108 reported cases of chordoma, 63 of which were in the sacrococcygeal region. Three cases of the latter type in infants are reported. The diagnosis may be furthered by the presence of physaliphores in the fluid obtained by puncture of the tumor. The typical cell is large, irregular and sharply defined, with a large vesicular nuclear. A mucinous substance accumulates in the cell in the form of large vesicles.

RALPH FULLER.

GRANULOSA CELL OVARIAN TUMORS AND PRECOCIOUS PUBERTY. EMIL NOVAK, Am. J. Obst. & Gynec. **26**:505, 1933.

Three cases of granulosa cell ovarian tumor are reported in girls from 3 to 6 years of age. The clinical features were precocious development of the secondary female characteristics and menstruation. Microscopically the tumor consists of granulosa cell rests left over from the formation of the follicular apparatus. Such tumors retain the function of producing the female sex hormone, and this fact explains the symptoms. An excess of the hormone in the child precipitates the changes of puberty.

JACOB KLEIN.

MELANOMA AND PIGMENTED MOLES. G. F. LAIDLAW and M. R. MURRAY, Am. J. Path. **9**:827, 1933.

Photomicrographs of silver-stained sections are presented to show that pigmented moles are rich in nerve fibers and tactile cells. End-bulbs of nerve fibers make contact with nevus cells exactly as they do with the tactile cells of the epidermis and hair follicles. Masson's observations of a profusion of structures resembling Meissner's tactile corpuscles in certain pigmented moles is confirmed. These moles, in elevation, pigmentation, innervation and grouping of tactile cells in the corium, bear a striking resemblance to the tactile spots of reptiles and Amphibia. In the course of evolution the reptilian tactile spots were replaced by mammalian hair follicles. The pigmented, hairy mole appears to be a link or transition from pigmented tactile organs of the reptilian type to hairy tactile organs of the mammalian type. In its hair follicles it is mammalian; in its pigmentation, elevation and groups of innervated tactile cells in the corium it follows the amphibian-reptilian pattern. Phylogenetic and ontogenetic hypotheses are presented.

AUTHORS' SUMMARY.

THE CYTOLOGY OF THE GLIOMA GROUP. L. B. COX, Am. J. Path. **9**:839, 1933.

One conclusion derived from this study is that names with an embryogenetic significance do not in all cases give the true values of the cells described. This in particular applies to the medulloblast and to certain of the spongioblasts and astroblasts. The neuroblast is also a cell that is particularly difficult to identify. It may be confused with included nerve cells, cells of the astroblast type and even with certain anaplastic, rapidly subdividing cells. The nature of a tumor is frequently more correctly interpreted by assuming that anaplastic changes have overtaken a well differentiated tissue than by ascribing it to differentiation of embryonal cells. The medulloblastoma of childhood, however, possesses certain qualities that suggest the possibility of an embryonal origin. The ordinary gliomas appear to fall into certain categories, as follows:

1. Tumors of adult tissue:
   - (*a*) Astrocytoma and its modifications
   - (*b*) Ependymoma and its modifications
   - (*c*) Oligodendroglioma
   - (*d*) Pinealoma
   - (*e*) Adult ganglioneuroma
2. Highly anaplastic tumors which may occur independently or in association with any of the foregoing tumors (glioblastoma multiforme)
3. Transitional forms between these:
   - (*a*) Astroblastoma
   - (*b*) Polar spongioblastoma
4. The medulloblastoma (possibly an embryonal tumor)
5. Rare tumors of the type of medullo-epithelioma and neuro-epithelioma, concerning which no opinion is expressed here

The mitotic figure content of such tumors offers the most accurate index of their activity, rather than deductions derived from their resemblance to embryonal cells. The difficulty in distinguishing between neoplastic cells and those that are derived from the glial tissue is discussed in some detail. The great advantage of post-mortem material as opposed to operative fragments is here apparent.

AUTHOR'S CONCLUSIONS.

FIBROMA OF THE BREAST. B. HALPERT and D. L. DIAL, Am. J. Path. **9**:905, 1933.

A pure fibroma of the breast, one of the few ever recorded, is reported. It occurred in a woman 47 years of age. The same breast on two previous occasions was the site of neoplastic growth. The structure of the tumor removed at the

first operation is not known. The growth removed at the second operation was a fibro-adenoma. The one removed at the third operation was a pure fibroma in which the neoplastic tissue closely resembled the stroma of the second growth.

AUTHORS' SUMMARY.

LIPOSARCOMA. F. A. FENDER, Am. J. Path. **9**:909, 1933.

A case of liposarcoma with late intracranial metastases is reported. The few cases available for study seem to indicate that these tumors grow slowly, are radiosensitive, metastasize late and show a tendency to metastasize to the cranium.

AUTHOR'S SUMMARY.

CARCINOMA OF THE TUBES AND OVARIES SECONDARY TO CARCINOMA OF THE BODY OF THE UTERUS. JOHN A. SIMPSON, Am. J. Path. **10**:1, 1934.

Carcinoma of the body of the uterus may extend through the wall to pelvic structures adherent to the uterus, and cancer cells may fall into the peritoneal cavity and give rise to implantation carcinoma. The lymphatic and the venous sinuses of the uterus may be invaded by carcinoma, and secondary carcinoma of the tubes and ovaries may arise from permeation of the lymphatics, also from cancer emboli. By continuous extension of carcinoma of the body of the uterus the mucosa can be replaced by the growth, which may extend into and replace the mucosa of the uterine portions of the tubes; here particles may be broken off and give rise to superficial carcinoma in the mucosa of the tubes, in the fimbriae and on the ovaries and peritoneum. In like manner parts of the uterine carcinoma may become implanted in the uterine and cervical mucosa and in wounds of the vagina and the abdominal incision. This article is illustrated by 38 plates with 113 figures.

INJURY AS A CAUSATIVE FACTOR OF MALIGNANT TUMORS. W. B. COLEY and N. L. HIGINBOTHAM, Ann. Surg. **98**:991, 1933.

From a study of 205 cases, Coley and Higinbotham conclude: 1. A single local trauma may be an important factor, probably the determining factor, in the development of a malignant tumor of any type. 2. Trauma is a causative factor in a larger proportion of cases of sarcoma than of carcinoma, and in a larger proportion of cases of bone sarcoma than of soft-part sarcoma. 3. The interval of time between the injury and the appearance of the tumor is often much shorter than is recognized by most writers. In the majority of cases the tumor develops within the first month or six weeks after the injury, but in a considerable number of cases it may develop within one or two weeks. The latter cases justify classification as instances of acute traumatic malignant conditions, as originally suggested by English surgeons. 4. While courts and compensation bureaus both in this country and in Europe have generally recognized single trauma as a competent producing cause of malignant tumor, it is only fair to the insurance carriers that each case be studied and judged on its own merits. 5. If the case in question fulfils all the conditions laid down by Segond, a causal relationship between the injury and the tumor must be admitted.

MULTIPLE GANGLIONEUROMA OF THE SKIN. H. MONTGOMERY and PAUL A. O'LEARY, Arch. Dermat. & Syph. **29**:26, 1934.

A man, aged 27, presented discrete, round, firm, reddish papules, from 1 mm. to 1 cm. in diameter, which first appeared on the buttocks and then spread to the pubes, abdomen, axillae, back and neck. Sections showed infiltration by round cells, histiocytes and sympathetic ganglion cells. Later the ganglion cells degenerated, and the lesions practically disappeared. The authors believe that such a condition is due to a malformation in which the primitive neurocytes accompanying the superficial blood vessels, or independent of them, develop into ganglion cells.

The patient also showed incomplete rotation of the colon with an increase of the ganglion cells of the appendix. A review of the literature failed to disclose a case comparable on the basis of clinical and histopathologic features.

S. W. BECKER.

BLOOD LIPIDS IN XANTHOMA. J. C. MICHAEL and H. O. NICHOLAS, Arch. Dermat. & Syph. **29**:228, 1934.

Total lipids, neutral fats, soaps and fatty acids, phosphatides and cholesterol were determined in the blood of four patients with xanthoma multiplex and five with xanthelasma. The lipid constituents of the blood showed an abnormal distribution. This, of course, confirms the findings of Bloch and Schaaf and Werner. Michael and Nicholas attempted to prove or disprove the theory of Schaaf and Werner that an instability of the oil-water emulsion exists in the blood of patients with xanthoma. They endeavored to break up the emulsions in these cases on the theory that if they were unstable they would be broken up more easily than the emulsions that exist in normal serums. Attempts to do this in several ways failed. They believe, therefore, that there are many other constituents in the blood serum which may play a major part in the production of a stable or an unstable oil-water emulsion, e. g., the serum proteins, calcium and sodium soaps of the fatty acids and other unknown emulsifying or de-emulsifying agents.

S. W. BECKER.

MULTIPLE CARCINOMA AND PIGMENTARY DERMATOSIS IN A NEGRO BOY. R. HOPKINS and M. T. VAN STUDDIFORD, Arch. Dermat. & Syph. **29**:408, 1934.

An unusual case of multiple squamous cell carcinoma, in a Negro boy, aged 4, is reported. Pigmented macules had developed on his face at the age of 1 year. About this time a wartlike tumor developed on the left lower eyelid. A second warty growth appeared on the nose and grew rapidly, projecting 1 cm. above the surface of the skin. The pigmented macules then appeared over the neck, arms, hands and legs. At the age of 4½ years three or four tumors developed on the face, enlarging and becoming ulcers. They progressed rapidly, and in spite of radium treatments he died four months after admission. Section of the tumors showed squamous cell carcinoma. In discussing the pigmentary dermatosis, xeroderma pigmentosum and arsenical pigmentation were considered. At autopsy no mestastatic lesions were found.

S. W. BECKER.

MEDULLOBLASTOMA (GRANULOBLASTOMA) OF THE CEREBELLUM. L. STEVENSON and F. ECHLIN, Arch. Neurol. & Psychiat. **31**:93, 1934.

Stevenson and Echlin describe six cases of tumor of the cerebellum which, in their opinion, originated from the granular layers. For this reason they suggest the name "granuloblastoma." Two such tumors have been previously described by them as medulloblastoma. The granuloblastoma, they think, grows from the cells of the external surface of the cerebellar leaflets, the so-called external granular layer, and pushes them apart. The cells of the tumor are round, possess little cytoplasm and greatly resemble neuroblasts. The tumor is rich in connective tissue.

GEORGE B. HASSIN.

Medicolegal Pathology

FORENSIC APPLICATION OF INDIVIDUALITY TESTS. K. LANDSTEINER, J. A. M. A. **103**:1041, 1934.

In this review by the discoverer of the blood groups the scientific basis for the medicolegal application of blood grouping is concisely presented. Bernstein's

theory that the four blood groups are inherited by means of three allelomorphic genes, A, B and R, is now generally accepted. With regard to the agglutinogens M and N, the theory of heredity proposed by Landsteiner and Levine, who discovered these agglutinogens in 1927, is undoubtedly correct, as evidenced in studies by eight independent workers on families including 2,447 children. According to this theory, the agglutinogens are inherited by means of a single pair of allelomorphic genes, M and N. The theory has also been confirmed by statistical data, and by investigations on more than 6,000 children and their mothers. The agglutinogens M and N have already been used in several hundred lawsuits involving the parentage of children, in Germany, Denmark and Sweden. By the combined use of the agglutinogens A, B, M and N, one of three men falsely accused of paternity can be exonerated. The presence of the agglutinogens A and B can be demonstrated by the absorption technic in old dried blood, in semen and in saliva. A number of authors have applied this method successfully in criminal cases. The properties M and N, though absent from semen and saliva, can be demonstrated in dried blood by the use of a suitable technic.

A. S. WIENER.

AGGLUTINOGENS M AND N IN BELGIUM. P. MOREAU, Ann. d. méd. lég. **14**:563, 1934.

The distribution of the MN types among 3,100 Belgians was as follows: type M, 28.89 per cent; type N, 20.77 per cent, and type MN, 50.33 per cent. There was no significant difference in the distributions in the two sexes at different ages or in patients with tuberculosis, syphilis, mental disease or cancer. The inheritance of the agglutinogens in 200 families with 739 children was in accord with the theory of Landsteiner and Levine that the transmission is by a single pair of allelomorphic genes. When 502 mothers with their 1,041 infants were examined, not once was a type M mother with a type N child or a type N mother with a type M child found.

A. S. WIENER.

IDENTIFICATION OF BLOOD GROUPS. J. JADIN, Arch. internat. de méd. expér. **9**:325, 1934.

The group to which spots of blood, urine or saliva belong can be determined by three methods based on the action of antihemolysins, anti-agglutinins and iso-agglutinins. There is a close correlation between the groups found by identification of blood, urine and saliva. The most sensitive method for their determination is that of absorption with heterologous hemolysins. Results with group A antigens are more satisfactory than those with group B antigens because of the difficulty in obtaining anti-B hemolysins.

ELIZABETH MCBROOM.

THE USE OF COMMERCIAL SERUM, ANTI-M AND ANTI-N, FOR FORENSIC WORK. H. SCHACKOWITZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:363, 1934.

Commercial serum prepared by two different companies was tested. The serum in some of the vials was found to be of low titer, and some of the samples gave nonspecific reactions. Before using commercial serum for medicolegal work, therefore, the investigator must test it for potency and specificity.

A. S. WIENER.

THE STUDY OF SIGNS OF VITAL REACTION. K. WALCHER, Deutsche Ztschr. f. ges. gerichtl. Med. **24**:16, 1934.

The importance of signs of vital reaction in determining the mode of death is discussed with particular reference to the possible crushing of dead bodies by railroad trains, trucks, etc. Walcher urges close study for hemorrhagic infiltrations into the muscles at points remote from the crushed areas and tears, for evidence of an absorption of blood in the diaphragm, and for signs of an aspiration of

brain substance. When death is supposed to have occurred without loss of blood, a marked anemia of the peripheral parts of the body as well as of the internal organs may be significant.

THE RÔLE OF CALCIUM CARBONATE IN THE CAUSTIC ACTION OF POTASSIUM CYANIDE. H. ELBEL, Deutsche Ztschr. f. ges. gerichtl. Med. **24**:25, 1934.

The caustic action of potassium cyanide depends on its alkaline nature. The action is not increased by calcium carbonate, as sometimes claimed, but rather is diminished.

THE GROWTH OF DECIDUAL TISSUE IN THE UTERINE WALL FOLLOWING INJURY IN ATTEMPTED ABORTION. NIPPE, Deutsche. Ztschr. f. ges. gerichtl. Med. **24**:30, 1934.

A case is described which illustrates the possibility that trauma of the uterine wall in attempted instrumental abortion may be followed by the growth of decidual tissue. The ectopic occurrence of decidual tissue and the production of decidua in animals by intra-uterine and extra-uterine injuries support this possibility. As in the case reported, the injury must have taken place some time before death, without immediate abortion and without complete perforation of the uterus.

RESULTS OF A SEROLOGIC STUDY OF THE POPULATION OF BERLIN. F. SCHIFF and A. HIEN, Klin. Wchnschr. **13**:375, 1934.

During a period of ten years the blood groups of 30,000 persons were determined by examining both the cells and the serum in each case. The following distribution of the blood groups was found: group O, 36.6 per cent; group A, 42.23 per cent; group B, 14.69 per cent, and group AB, 6.46 per cent. For these frequencies, $p + q + r = 1.0008$, so that these statistical data support the Bernstein theory of the heredity of the blood groups.

A. S. WIENER.

Technical

FRACTIONAL ULTRAFILTRATION. H. C. ALLISBAUGH and R. R. HYDE, Am. J. Hyg. **21**:64, 1935.

This paper presents an improved technic for the preparation of membranes of the Bechhold type. An improved calibrated holder for these membranes has been devised. This gives a series of efficient ultrafilters of graded porosity. A rotary collecting filter chamber has been constructed which facilitates the fractionation of filtrates under negative pressure so that the rate of flow and the titer of the filtrate can be readily expressed in terms of time. The results obtained with these improvements make possible the evaluation of certain problems that have arisen in ultrafiltration and the more accurate determination of the particulate size of dispersed particles in colloidal systems.

FROM THE AUTHORS' SUMMARY.

THE FRIEDMAN TEST IN PREGNANCY. M. A. GOLDBERGER, U. J. SALMON and R. T. FRANK, J. A. M. A. **103**:1210, 1934.

In 1,093 normal intra-uterine pregnancies the percentage of false positive Friedman tests was 0.09. The percentage of false negative tests was 0.55. This percentage of error is small as compared with the percentages reported by others, and the reduction is attributed to the fact that duplicate tests were made. At least 3.4 per cent of rabbits appear to be refractory to the Friedman test. In forty-four cases of ectopic pregnancy the percentage of false negative tests was 32. This high percentage of negative tests is accounted for by the presence of dead or degenerated villi. In both intra-uterine and extra-uterine pregnancies the Friedman test is dependent on the viability of the chorion. In missed abortion the

Friedman test may remain positive for as long as thirty days after the death of the fetus. In incomplete abortion the Friedman test may be positive. The presence of a viable fetus can be determined by study of the female sex hormone of the blood. In the diagnosis of ectopic gestation the Friedman test is of value only in cases in which it is positive. If the test is negative in a case of suspected ectopic pregnancy, the clinical history and observations should determine the diagnosis.

FROM THE AUTHORS' SUMMARY.

HIGH FREQUENCY CURRENTS FOR BIOPSIES. J. P. GUEQUIERRE and F. D. WEIDMAN, J. A. M. A. **103**:1693, 1934.

The objections of the pathologist to the use of coagulating currents can be largely overcome by adhering to the cutting current. The method is not infallible, owing to such factors as muscular twitch, unsteadiness of the hand or an anatomic location such as the face, which limits the removal to a very small specimen. Barring these conditions, the readiness of the apparatus, the bloodlessness of the operation, the insensitiveness to postoperative pain and the psychologic effect on the patient all contribute to securing a greater number of biopsies, which are sorely needed for the advance of dermatology in general, to say nothing of the assistance that accrues in confirming the diagnosis.

AUTHORS' SUMMARY.

ASPIRATION BIOPSY. H. E. MARTIN and E. B. ELLIS, Surg., Gynec. & Obst. **59**: 578, 1934.

The indications for biopsy by needle puncture and aspiration and the technic are described in detail. Over 1,400 positive histologic diagnoses have been made by this method at Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City.

AUTHORS' SUMMARY.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 27, 1934

NATHAN CHANDLER FOOT, *Vice-President, in the Chair*

IRVING GRAEF, *Secretary*

CONGENITAL APLASIA OF THE ISLANDS OF LANGERHANS WITH DIABETES MELLITUS. P. A. H. MIDELFART (by invitation) and ROBERT A. MOORE.

In some cases of diabetes mellitus in children a numerical decrease in the islands of Langerhans has been observed. In a few cases there are no demonstrable islands.

A girl, 13 years of age, was admitted to New York Hospital on the service of Dr. Eugene DuBois because of pain in the back. Her birth and the first year of life were uneventful. Near the second birthday the mother noticed polydipsia and polyuria. At 7 years of age there was noticeable failure of vision. At this time a diagnosis of diabetes was made.

No regular treatment had been instituted. Physical examination showed underdevelopment and undernourishment, bilateral cataract, a blowing apical systolic murmur, slight thickening and tortuosity of the peripheral arteries and underdevelopment of the external genitalia. The blood showed slight leukocytosis, moderate anemia and a slight elevation of blood urea nitrogen. The cholesterol was slightly elevated; the phosphorus and the calcium content were normal. X-ray photographs of the long bones showed slight decalcification. The urine contained streptococci in pure culture and many pus cells. It contained less than 4 rat units of ovarian follicular hormone per liter.

The urinary infection was controlled by drainage and irrigation; the diabetes, with difficulty by diet and insulin. Three months after admission to the hospital the child died after a convulsion of unknown cause.

At autopsy the urinary tract was seen to be the seat of a chronic suppurative inflammatory process. The genitalia were infantile, and the ovaries contained no follicles. The thyroid gland, thymus and adrenal glands were normal. A count of the cells of the pituitary gland showed 58.2 per cent chromophobes, 27.8 per cent acidophils and 14 per cent basophils (16,755 cells counted). The pancreas grossly was slightly decreased in size, and microscopically revealed only very few structures similar to islands. The structure of this organ as a whole was immature; there was abundant stroma, but no evidence of recent or old inflammation.

It is concluded that the diabetes in this child was dependent on congenital aplasia of the islands of Langerhans, and that death was due to the urinary infection.

METASTASIZING TUMOR OF THE PINEAL BODY. ALFRED PLAUT.

An Austrian hatter, 33 years old, was treated for a hypophyseal syndrome four years before his death. At that time he complained of polyuria, poor vision and loss of sex power. He received treatment with roentgen rays of high voltage; the polyuria disappeared; his vision improved sufficiently so that he could return to work, but sex power was not restored.

About two and a half years later he noticed pain in the back, starting at the neck and radiating downward; numbness of the hands and feet followed. His inability to walk finally brought the patient to the hospital, where, during his two months' stay, he offered a variety of neurologic symptoms which led to the assump-

tion of a widely distributed cerebrospinal lesion of unknown character. There were no symptoms pointing to a focus. The search for tubercle bacilli showed none. The Wassermann reaction was negative. As the patient was a hatter, a suspicion arose that poisons used in his profession might have caused polyneuritis, but the powders which the patient used and the scalings from his hyperkeratotic hands and feet did not contain lead, arsenic, mercury or antimony. His spinal fluid contained several thousand cells, but no definite diagnosis could be made from their character. There was no block. The visual fields were slightly contracted concentrically; both pupils were almost fixed to light; there was almost complete optic atrophy. Limitation of upward and inward movements of the right eye was noted. In the last two weeks before death the patient became disoriented and psychotic. At this time all forms of sensation were disturbed. There was ophthalmoplegia. Meningitic symptoms were absent.

The following diagnoses were considered during the course of the disease: an old pituitary lesion with probable superimposed neuronitis, chiefly motor; a glioma of the optic nerves; arsenical poisoning; a diffuse infectious lesion of the central nervous system; sarcomatosis of the meninges, and leaking suprasellar cyst.

At autopsy the brain and its meninges showed nothing remarkable grossly. The cranial nerves, notably the oculomotor, trigeminus and facial, were much thicker than normal. The optic nerves were atrophic. The olfactory nerves were normal. The thickening of nerves on the left side was slightly more marked than that of nerves on the right. On slicing the brain, which was fixed in solution of formaldehyde, distention of the ventricles was noted. Only at a later reexamination an indefinite, not at all remarkable mass of tissue was discovered in the surroundings of the vena magna. There was no circumscribed tumor in the region of the pineal gland.

On the inside of the lumbar dura mater, occasional flat gray elevations, measuring up to 1 cm. in diameter, were seen. The spinal meninges appeared opaque in spots. The spinal ganglions were thickened and firm. They were about three times as large as normal. Their cut surfaces were grayish white and had no markings. The filaments of the cauda equina were thickened throughout. The conus terminalis looked normal.

Microscopic examination of many different pieces gave a rather uniform picture. The brain and spinal cord proper were not infiltrated except for the perivascular spaces in the superficial layers. The soft meninges, however, and the nerves were diffusely infiltrated and widely destroyed by a peculiar tissue which consisted of large and small cells, but did not show any stroma. These two cell types resembled the two kinds of cells that are found in the pineal gland and in tumors of the pineal gland. The small cells were slightly larger than lymphocytes; they were not round, but irregularly ovoid, sometimes dumbbell-shaped. Their nuclei were not so rich in chromatin as the nuclei of lymphocytes are. Some of the large cells definitely resembled the large cells of the pineal gland, with indistinct cytoplasm, large nucleus and large deep-staining nuclear inclusion.

In the region of the pineal gland, a nodule the size of a small bean was situated. It contained acervulus. It was infiltrated by tumor as described, and on serial section remnants of the connective tissue of the adult pineal gland could be demonstrated. Tumor was found also in the choroid plexus of the fourth ventricle. The infundibulum and tuber cinereum, in relation to the tumor, did not differ from other portions of the brain. At the roots of the cerebral nerves, a sharp borderline between the intact brain tissue and the tumorous nerve tissue was present.

It must be assumed that the tumor cells had been distributed by the spinal fluid. This mode of metastasis has been described for tumors originating from the choroid plexus. Only one case is on record (that of Berblinger) in which a tumor of the pineal gland metastasized in this fashion. Aside from the fact that in Berblinger's case a large tumor of this gland was present, the two cases are almost exactly alike in every detail, including the age and sex of the patient.

The tumor is called "pinealocytoma" ("a tumor formed by the cells of the pineal gland") without any attempt at classification.

DISCUSSION

IRVING GRAEF: Did Dr. Plaut notice any chromophilic granules in the cytoplasm of these cells? How did the tumor cells behave with acid and basic dyes?

ALFRED PLAUT: Many experiments in staining were made with these cells, but none of the stains used gave better information than the hematoxylin-eosin stain. Silver stains were applied. No luck was had with the Río Hortega method, but I must add that no luck was had with this method when it was applied to normal pineal glands. No stain for special granules was applied. Several silver stains were used. It was not possible to demonstrate prolongations of the large cells with phosphotungstic acid-hematoxylin.

MILTON HELPERN: How striking was the lesion in the pineal gland?

ALFRED PLAUT: You mean microscopically?

MILTON HELPERN: Yes.

ALFRED PLAUT: It was exactly the same tumor that I saw in all the other sections. There was an indefinite mass in the surroundings of the vena magna, and in the region of the pineal gland, attached to normal habenula, there was a mass about the size of a bean. In the first sections cut the tissue consisted of tumor only. On continuing I found some dense stroma which I took for the remnant of the normal pineal gland.

THE INFLUENCE OF DINITROPHENOL ON CARBOHYDRATE METABOLISM. MAX WISHNOFSKY, ARTHUR P. KANE, EDMUND L. SHLEVIN and CHARLES S. BYRON (by invitation).

The prevailing opinion is that all measures, except exercise, which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient for carbohydrates. In dinitrophenol one has an ideal substance with which to test the validity of this conception, for, in the words of Hall, "Dinitrophenol is well adapted to the experimental study of the various responses of the organism to conditions of accelerated tissue metabolism." The following is a summary of our findings and conclusions:

In normal persons dinitrophenol causes a significant increase in the concentration of the blood sugar both at the fasting level and after the ingestion of dextrose. In the present state of knowledge, the causative mechanism cannot be determined. The elevation of the blood sugar level in hyperthyroidism, hyperepinephrinism and other conditions in which there is an augmentation in the production of heat must in part be attributed to the increase in oxidative metabolism.

Dinitrophenol does not cause any significant change in the concentration of blood sugar in diabetes mellitus, either at the fasting level or after the ingestion of dextrose. There is, however, a decided reduction in glycosuria after the administration of dextrose, which is to be explained on the basis of an elevation of the renal threshold for dextrose. These findings offer direct proof that an increase in oxidative metabolism does not cause a depreciation in tolerance for carbohydrates in diabetes mellitus. The decrease in tolerance which occurs in diabetes mellitus associated with hyperthyroidism and other conditions in which there is an increase in heat production must be ascribed to other factors.

The findings reported are not to be taken as a brief for the use of dinitrophenol. The sole purpose of this work was to study the influence of increased production of heat on carbohydrate metabolism.

MENINGO-ENCEPHALITIS CAUSED BY CYSTICERCUS CELLULOSAE. VERA B. DOLGOPOL and (by invitation) MARCUS NEUSTAEDTER.

This article was published in full in the *Archives of Neurology and Psychiatry* (**33**:132, 1935).

A Mexican woman, 31 years old, who suffered from persistent headaches and transient impairment of vision in the left eye, vomiting and convulsions, followed by impairment of vision in the right eye, showed for a few weeks eosinophila in the blood (10 per cent) and in the cerebrospinal fluid (up to 26 per cent). No

ova were found in the stools, nor hooklets in the spinal fluid. The progressive impairment of vision was accompanied by generalized clonic convulsions. After the operation of decompression a paralysis of the left side of the body developed. The patient died one year and nine months after the onset of the illness.

Necropsy revealed plastic basal meningitis and a racemose cysticercus cyst of the base of the brain and of the right sylvian fissure. The exudate contained lymphocytes, plasma cells, round phagocytes with refractile granules, and foreign body giant cells; no eosinophils were found. No cysticerci were found in the ventricles or in the brain substance. The cyst wall showed the characteristic histologic structure (chitinous, nuclear and reticular layers). Intracystic structures resembling dead parasites were seen in two evaginations of the cyst. Reactive capsules surrounded several others. The cortex at the base of the brain and the ventricular walls showed perivascular infiltrations consisting of lymphocytes and plasma cells, with some glial reaction. A cortical and subcortical softening was present in the right hemisphere. The arteries at the base of the brain and the cortical branches of the right middle cerebral artery showed typical cysticercus arteritis. Arteries remote from parasites showed no changes. No tapeworm was found in the intestine.

DISCUSSION

PAUL KLEMPERER: Is the meningitis in cysticercosis limited to the vicinity of the cysts, or may it extend beyond them? Is the reaction of the brain in this case not unusually severe, or is such a severe encephalitis in cysticercus infestation usual?

VERA B. DOLGOPOL: In the case of a single cyst, the meningitis is usually limited to the immediate proximity of the cyst. When there are several cysts far apart on the convexities, the meningitis is also localized, but if the cyst occurs at the base, where it assumes a racemose form, the meningitis spreads beyond the presence of the cysticercus. About the severity of the encephalitic changes, similar changes on the surface of the ventricles have been described, but in our case they were more extensive than usual.

J. M. RAVID: Can you explain the exact localization of the parasites in the brain?

VERA B. DOLGOPOL: I do not think in general very much is known as to how the parasite reaches any organ. One cannot say anything definite about the reason why it comes to the brain. The racemose character of the cyst at the base of the brain is explained largely by the width of the meningeal spaces there, which give the cyst room to form evaginations and a chance to twist around. As to how the parasite reaches the brain and by what it is directed there, there is no definite information.

AN OSTEOPLASTIC TUMOR OF OBSCURE ORIGIN AND RELATIONSHIP. SHELDON A. JACOBSON.

A woman, 29 years of age, was admitted to the Hospital for Joint Diseases on Aug. 15, 1932, with a chief complaint of pains in the back.

Four years previously, following a fall, constant pain in the back and left shoulder set in. A physician diagnosed arthritis. In October 1931, the pains became increasingly severe. In April 1932 a cold in the head accompanied by shooting pains caused a sudden severe illness. The patient was taken to Beth-El Hospital unconscious. There, after she had been in stupor for a few days, head traction was instituted. After seven weeks she was discharged, her shooting pains gone, the others persisting. Braces were prescribed by an outside physician. The pain became steadily worse, constant and pounding on motion; a swelling appeared. Dr. Wishner referred her to the Hospital for Joint Diseases.

At a point from ½ to 1 inch (about 1.3 to 2.5 cm.) to the left of the midline, overlying dorsal vertebrae V to VII, was a soft, very tender mass measuring 3 inches (7.6 cm.) in length, which was neither hot nor red. It was excised and found to lie very close on, though it was not continuous with, the vertebral

laminae. It was a fairly firm yellowish-white encapsulated tumor, in the middle of which was an area of hard, gritty substance.

Microscopic section showed a very well encapsulated mass of tumor tissue. It was for the most part a homogeneous, parenchymatous, very closely packed aggregation of remarkably isomorphic cells. These consisted of small polyhedral pyknotic nuclei with very little and very difficultly perceptible cytoplasm. They were arranged, as shown by the Laidlaw stain, in clusters of six to eight, the clusters, but not the individual cells, being enclosed by silver-staining fibers. The nuclei themselves were likewise silver-positive. (This denotes, according to Laidlaw, that the cells were not of connective tissue or of endothelial origin.) There were, curiously enough, several extensive areas of cartilage and bone formation. This seemed to be the result of direct metaplasia of the tumor cells themselves; there was no indication that they were passing through a spindle cell stage, nor did the very scanty stroma seem to participate in the process.

A tentative diagnosis of metastatic osteogenic sarcoma was made; after an exhaustive roentgenographic study of the skeleton, the results of which were completely negative, this diagnosis was changed to one of osteoblastoma. Additional treatment by radium pack was given.

Pain soon recurred. In August 1933, the patient was readmitted to the hospital with a local recurrence. A second operation showed the tumor invading the spinous process and the posterior portion of the neural arch of dorsal vertebra IV. Microscopic study showed the same morphology as before, except for the absence of a capsule.

Despite treatment with radium and x-rays symptoms continued. In September 1934, an x-ray photograph showed compression and porosis of the body of dorsal vertebra IV. Symptoms and signs of a fairly complete transverse compressive lesion of the spinal cord appeared. Death ensued in October 1934.

Autopsy showed the original tumor mass to be limited to what was left of the spinous process of dorsal vertebra IV, with very slight infiltration of the body posteriorly. The tumor bulged markedly into the neural canal, compressing the cord against the anterior wall. Metastases were present only in the lungs, in the form of several discrete nodules; their histology corresponded with that of the parenchyma of the original tumor; cartilage was being formed in one. There were acute cystitis and bilateral pyelonephritis.

The cytology of this tumor corresponds to that of endothelial myeloma, but its osteoplastic and chondroplastic properties rule out this diagnosis. It is my opinion that the tumor is one of the preconnective-tissue mesenchymal cells, with the ability to differentiate at any point and in any of several directions.

DISCUSSION

PAUL KLEMPERER: Will Dr. Jacobson express an opinion as to the relation which this tumor bears to the so-called Ewing tumor, and further state whether he thinks the Ewing tumor can also occasionally give that picture of bone formation?

ALFRED PLAUT: I should like to know if Dr. Jacobson considers the cartilage-like tissue found in tumors of salivary glands true cartilage.

JACOB FURTH: There is a transmissible chicken tumor composed of round cells which form bone and cartilage. The tumor is produced by a virus. A study of it might yield information concerning the nature of the round cell tumors that form bone and cartilage.

SHELDON A. JACOBSON: Dr. Plaut's question is difficult to answer. It often occurs when one is studying slides, particularly in considering such a disease as arthritis, that it is impossible to satisfy oneself completely as to whether one is dealing with cartilage, bone or osteoid tissue, or possibly something else; therefore any opinion as to whether a given tissue is cartilage or not can be only an opinion. If it looks sufficiently like the cartilage cells, one is generally justified in assigning it to that group; therefore my answer to the question as to whether I consider the matter developing in mixed tumors of the salivary glands cartilage will be an affirmative one. I do consider it such.

As to the question of the relationship of this tumor to the Ewing tumor, that also is difficult, because the nature of the Ewing tumor is by no means definitely established. It is usually considered a tumor of the endothelium of blood or lymph vessels. I think that that has been fairly well proved by the number of transitions which have been seen between incontrovertible hemangioma and Ewing tumor. Assuming this, I think one can draw a phylogenetic line. First comes the mesenchymal cell. This differentiates into two general types, the connective tissue type (fibrous tissue, bone, cartilage and so forth) and the marrow and endothelial type. The tumor which I have presented, I should say, occurs just before the point at which the two lines branch, and in its manifestations some of its cells go on to form bone and cartilage. The Ewing tumor, on the other hand, occurs a considerable distance down along the other branch, namely, the branch which leads from mesenchyme to endothelium. This brings one to the matter of bone formation in Ewing's tumor. This does indeed occur, but critical histologic examination gives the impression that this is the result of the tumor's stimulation of previously present osteoblastic cells; the tumor cells themselves do not seem to undergo such differentiation.

The comparison with the chicken tumor, made by Dr. Furth, is suggestive. I have not seen that tumor. I am not familiar with the exact morphology of its cells. I cannot, therefore, say in what respect it might resemble this tumor.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Jan. 14, 1935

I. Pilot, *President, in the Chair*

Edwin F. Hirsch, *Secretary*

Dissemination of Human Pathogenic Bacteria Through the Cow's Udder.

D. J. Davis.

The numerous milk-borne outbreaks of disease have focused attention on the mechanism of infections of the cow's udder. Tubercle bacilli, Brucella abortus and possibly paratyphoid bacilli reach the udder from the interior, that is, from the blood stream or tissues of the cow. Other bacteria, notably streptococci and possibly staphylococci, may reach the udder through the lactiferous ducts of the teats.

Outbreaks of septic sore throat traced to milk have at times followed injury of the teats, but often no history of such injury is obtainable. There is no evidence that hemolytic streptococci reach the udder from the blood stream or tissues. When no history of injury to the teats is obtainable it is assumed that streptococci have been implanted on the skin of the teat from some human source and have ascended the duct to the milk cisterns. Experimental placing on the teat of hemolytic streptococci causing sore throat is followed by definite streptococcus mastitis in a short time.

Sections of the cow's teat reveal a dense squamous cornified epithelium lining the lactiferous duct around which the muscle sphincter is located. The epithelial surface of the duct, which varies from 0.6 to 1 cm., is rough and irregular furnishing small pockets and crevices in which the milk may be retained. It is along such a channel that the streptococci ascend by growth, their ascent being possibly aided by manipulation. In most teats the sphincter is adequate to prevent leakage. Not infrequently, however, it becomes incompetent, and as the tension of the milk in the cisterns increases, the milk trickles through, creating a direct route through the meatus to the exterior through which bacteria may enter.

As to whether a lack of pressure in the udder and therefore suction during the process of milking may occur was tested in a series of thirteen milch cows by inserting the end of the teat in a dye (carbolfuchsin) as the pressure on the

teat was released. The cows were then immediately slaughtered and the teats examined. In no instance did the dye ascend in the lactiferous duct more than one-half the distance to the cistern, even in a leaking teat.

In an udder used as the site of experimental mastitis no changes of any importance indicating involvement of the lymphatics or subepithelial tissue were noted about the meatus or along the epithelium of the duct.

The main body of the udder in experimental human streptococcic mastitis reveals extensive inflammatory changes.

The streptococci used in the experiments were isolated from outbreaks of septic sore throat; they were encapsulated and revealed the large moist watery or mucoid growth. These streptococci, to which the term Streptococcus epidemicus has been applied, ferment trehalose but do not ferment sorbitol. It is assumed that they are of human origin.

Attention is called to the fact that in most outbreaks of udder-borne septic sore throat no cases of scarlet fever appear. Erysipelas as a complication occurs in a few cases. In epidemics of udder-borne scarlet fever, such as the outbreak in New Jersey, nearly all cases have been typical, and relatively few cases of septic sore throat have appeared.

As these accidental human experiments on udder-borne disease represent such a vast scale and such great virulence they should be valuable criteria in determining the specificity of streptococci. Practically all biologic and laboratory tests, except possibly the specific toxin test for scarlet fever streptococci, are more or less variable. This is true even of the hemolytic reaction, as Pilot has shown.

DISCUSSION

E. F. HIRSCH: In the light of recent studies demonstrating toxic properties in filtrates of broth cultures of certain bacteria, what probability is there that milk adequately pasteurized may cause gastro-enteritis?

O. T. SCHULTZ: Does milking by machine increase the chances for infection?

D. J. DAVIS: Pasteurization, of course, decreases the danger of milk-borne gastro-enteritis. Through milking by machine better and cleaner milk is obtainable.

I. PILOT: I know of an instance of bovine mastitis in which human hemolytic streptococci were excreted for a long time.

AN ANENCEPHALIC MONSTER WITH "RHINODYMIE" AND OTHER ANOMALIES. SAMUEL B. BRODER.

The term *"rhinodymie"* is used as originally defined by Lesbre and Forgeot to indicate a "doubling only in the nasal region; occasionally a third eye, the upper jaw mostly incompletely doubled." Various theories pertaining to the etiology of monstrosity were reviewed and analyzed; particular stress was laid on the contribution of experimental embryology as it is best exemplified in the works of Stockard and Child and their students. The relationship of the endocrine glands to the development of monsters was then discussed, and the incidence of anencephalic births in families was considered.

A Negress, secondipara and tertigravida, was admitted on August 23, 1932. Physical examination and serologic tests of the blood gave negative results. A diagnosis of polyhydramnios was made, and labor was induced. Two days later the membranes ruptured spontaneously, and five hours later she was delivered of a female anencephalic monster. Five minutes later the placenta was delivered. The placenta and the cord were normal. The body of the monster was full grown and weighed 5½ pounds (2,496 Gm.). It began to breathe spontaneously and lived for an hour and eight minutes. The body was placed in formaldehyde, and necropsy was performed three weeks later.

In lieu of the calvarium there was a hemorrhagic soft membrane which extended from a region just above the eyes to a level corresponding to the occipital protuberance. The region of the nasal septum was depressed and was continuous with a groove running down a medial elongation of the upper lip which was fused with the lower lip on the left side only. It formed the median boundary of a blind oval pouch. This pouch was 12 mm. deep, and within it was a tonguelike

tissue 2 mm. long which was made up of stratified squamous epithelium and fibrous connective tissue without glands or muscle tissue. The lining of this accessory mouth had the appearance of an oral cavity. The cerebrum, cerebellum and hypophysis were absent. The medulla oblongata was intact. Both optic, both infra-orbital and the seventh and eighth nerves were recognized. The right eye showed marked postmortem change, and the structures of the left eye, with the exception of the iris and ciliary body, were well developed. The abnormalities of the ears consisted of bilateral deformities of the stapes and abnormalities of the meatus and modiolus. The right lung had four lobes; the left had three. The abdominal cavity was separated from the thorax by an abnormal diaphragm the two halves of which were not in the same plane, the right being lower than the left, as a result of which the spleen was in the thorax. The esophagus dilated into an imperfectly developed stomach which was partially located in the thorax. Both the large and the small intestine were attached posteriorly by a common mesentery. No suprarenal tissues were found.

The following conclusions were reached:

This monstrosity belongs in the group of *"rhinodymie"* as described by Rating.

The anatomic changes and the consideration of cases described in the literature suggest that doubling of the nose and of the mouth are expressions of a tendency toward dicephaly. In this instance these abnormalities were associated with anencephaly, spina bifida and a defect of the diaphragm.

Experimental evidence, which alone is significant, indicates that anencephaly is due to an inhibition in the early development of the embryo affecting regions of the highest rate of development. The frequent association of anencephaly with cephalic duplications suggests that the latter may be due to similar factors.

The abnormality of the diaphragm may be interpreted as an interference with the development of the pleuroperitoneal membrane.

Attention is called to the futility of much of the speculation concerning the causes underlying the development of human monsters. The only direct evidence bearing on the subject at the present time is that of experimental embryology.

FATE OF DETACHED ARTICULAR CARTILAGE. D. B. PHEMISTER.

Bone bordering on a joint and covered by articular cartilage not infrequently is detached by injury which completely interrupts its blood supply. The fate of the bone is well known, but that of the articular cartilage has not been determined. Studies have been made of such cartilage both in cases of intra-articular fractures, such as fractures of the neck of the femur, and in experiments with animals. The bone and bone marrow of the detached piece undergo necrosis with disappearance of cells. If the fragment becomes attached either to its bony bed, which is usually the case, or to the capsule, there follows a gradual invasion by new blood vessels and fibrous tissue, and the dead marrow is replaced by fibrous marrow. Then follows the growth of a zone of replacement of the dead and fibrous marrow by living bone and hemopoietic marrow. This may take from a few weeks to a few years, depending on the size of the fragment and on whether or not bony union is established. The articular cartilage of such a fragment retains its power to take on stain for a period varying from a few weeks to several months, depending on the case. If the underlying bone is reinvaded and replaced by living bone and marrow during that period the nutrition of the cartilage is restored to normal and the cartilage remains in a living healthy state, but if the bony transformation is delayed for several months the cells of the cartilage suffer nutritional changes and stain poorly because the synovial fluid cannot keep them well nourished over a long time. However, if the underlying bone is transformed during that period the cartilage cells immediately receive adequate nutrition, come out of their quiescent state and return to normal. If the transformative process in the bone is delayed for a year or more the cartilage dies and is eventually absorbed and replaced either by fibrocartilage or by fibrous tissue.

Fragments of articular cartilage rarely are detached alone or with only a small fragment of underlying bone and become loose bodies in the joint. There is a growth of fibroblasts about their periphery, nourished by synovial fluid, and a

gradual transformation into fibrocartilage occurs. Such bodies may increase in size slowly and eventually undergo partial calcification or ossification. The cells of the original articular fibrocartilage slowly become necrotic and are absorbed and replaced by fibrocartilage.

DISCUSSION

I. PILOT: Is the cartilage affected in bones with atrophy of disuse?

D. B. PHEMISTER: The bone may undergo marked atrophy through disuse; even the cortex may be affected, but the cartilage is not absorbed to any extent. Occasionally in cases of extreme atrophy there is some invasion by bone.

CHEMICAL NATURE OF TOBACCO MOSAIC VIRUS. JORGEN M. BIRKELAND.

Barton-Wright and McBain claim to have succeeded in obtaining tobacco mosaic virus in a crystalline form, free from nitrogen and highly infectious. The results I have obtained indicate that the crystals in question are phosphate crystals. These results are in agreement with those of Caldwell as reported in *Nature*, Feb. 3, 1934. I have found, furthermore, (1) that when the salts are removed from the phosphate eluate by electrodialysis, no crystals are formed on the addition of acetone and (2) that when the crystals obtained on the addition of acetone to the phosphate eluate are electrodialyzed they disappear and do not reappear on the further addition of acetone. Quantitative tests for the presence of virus indicate no diminution following the removal of the crystals. It is suggested that the virus may act as a crystallization nucleus.

The viruses of tobacco mosaic and of several other plants are antigenic and produce precipitins and complement-fixing antibodies and are, therefore, probably of the nature of protein.

ANOMALIES OF THE CIRCLE OF WILLIS AND THE RESULTING VASCULAR DISTURBANCES OF THE BRAIN. OTTO SAPHIR.

Anomalies of the circle of Willis with resulting interruption of the circulation between the internal carotid and the vertebral artery may form the anatomic basis of cerebral vascular disturbances. The recognition of such anomalies is significant because they aid in the explanation of cerebral hemorrhage and encephalomalacia on morphologically demonstrable grounds in the absence of occluding lesions of the supplying arteries. This seems the more important because of the present-day tendency to explain symptoms and also morphologic changes on the basis of functional disturbances of the circulation. Three brains are described which revealed anomalies of the circle of Willis involving the posterior communicating arteries and an abnormal origin of the posterior cerebral artery in one instance. Two of these brains revealed areas of encephalomalacia and cerebral hemorrhage, without the presence of occluding lesions in the supplying arteries. Whereas the posterior communicating arteries are not essential to the maintenance of the circulation in the brain under normal conditions, a free unhampered collateral anastomosis between the internal carotid and the vertebral artery is important in instances of diffuse arteriosclerosis of the arteries of the base of the brain combined with beginning myocardial failure.

DISCUSSION

A. WEIL: It is tempting to conclude from certain physiologic or anatomic changes observed in the brain that the vascular anomalies are responsible. One should know, however, how often such anomalies occur without the lesions noted. Many normal variations have been observed, and one must be careful in drawing conclusions.

I. PILOT: Were any of the hemorrhages of vital significance?

OTTO SAPHIR: Many normal variations in the vascular bed have been noted, and in a given case other factors such as cardiac incompetence may enter. The decrease in vis a tergo may be enough to cause encephalomalacia. Probably some of the hemorrhages were capillary or venous.

Book Reviews

Rats, Lice and History: Being a Study in Biography, Which, after Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals with the Life History of Typhus Fever. By Hans Zinsser. Cloth. Price, $2.75. Pp. 301. Published for the Atlantic Monthly Press. Boston: Little, Brown & Company, 1935.

This is a most interesting book on the history of typhus fever, but many other topics are discussed as well. The book was "written at odd moments as a relaxation from studies of typhus fever in the laboratory and in the field." No disease illustrates better than typhus the evolution of parasitism and the effects of epidemics on human events, and from his point of view no better or more competent account of typhus exists than this book. The larger part of the book is designed to prepare the lay reader for final chapters that deal directly with typhus. In these preliminary chapters a variety of subjects more or less pertinent to the main topic are considered. The right of the bacteriologist to enter the popular field of biography with the story of typhus is upheld. Then the relationship between science and art receives attention. Bacteria and other parasites are defined, with remarks on the problem of the origin of life. Coming gradually closer to typhus (the book has been called a "masterpiece of the roundabout"), parasitism in general is considered. The changing nature of infectious diseases as revealed in the history of epidemics is discussed. A chapter is devoted to so-called new diseases and to certain diseases that seem to have disappeared. There are chapters on the epidemics of the ancient world, on the relation of epidemics to the fall of Rome and on the influence of epidemic diseases on political and military history, with a digression on the relative unimportance of generals. The louse, which "shares with us the misfortune of being prey to the typhus virus," receives detailed consideration from all sides, and there is also much about rats as well as a little about mice, but the rat flea escapes with mere mention. In view of the attention paid to the louse, the flea has reason to be jealous. "Man and the rat will always be pitted against each other as implacable enemies, and the rat's most potent weapons against mankind have been its perpetual maintenance of the infectious agents of plague and typhus fever." Then the biography of typhus begins. Its "birth, childhood and adolescence" are sketched; its earliest epidemic exploits are told; full account is rendered of its young manhood and the period of early vigor and wild oats, and finally comes the "appraisal of a contemporary and prospects of future education and discipline."

This is a remarkable book. It will be read widely for its own sake. Indeed, at the time of the writing of this review it is listed as a best seller. While richly and competently informative in its special field, the literary skill, the clever discursiveness and the humor and wit make it enjoyable reading. It is pleasant to record that literary recognition has been achieved by an able investigator and teacher of bacteriology.

Recherches expérimentales sur quelques esters de la choline. By Maurice Villaret, professeur à la Faculté de médecine de Paris; L. Justin-Besançon, médecin des hôpitaux de Paris, and René Cachera, chef de clinique à la Faculté de médecine de Paris. Paper. Price, 38 francs. Pp. 254, with 79 illustrations. Paris: Masson & Cie, 1934.

After two introductory chapters on the history and chemistry of choline esters, the authors proceed to describe the actions of these compounds. The major portion of this stimulating monograph is divided into two sections: (1) the experimental effects on animals and (2) the effects on man.

The main thesis deals almost exclusively with the results obtained in the authors' laboratories. The majority of the studies were on dogs. The effect of

various derivatives of choline on the cardiovascular system, as well as the mechanism of the actions involved and the secondary secretion of epinephrine, is considered. Different routes of administration (intravenous, subcutaneous and jejunal) are evaluated. Among the substances used were acetylcholine, formylcholine, isobutyrylcholine, bromocholine, methylacetylcholine and carbamocholine. The effect on the respiratory system is also stressed. The influence on the smooth musculature of the biliary tract, bronchi and iris and the action on the salivary glands, pancreas, vagus nerve and various chemical constituents of the blood are briefly discussed. A representative experiment is described to illustrate the points in question. The modus operandi of synergistic and antagonistic drugs on the choline esters and the manner of destruction of the esters are well explained. The understanding of these factors is necessary for the comprehension of the fundamental mechanism underlying the action of vagomimetic substances.

The authors attempted to demonstrate the possible applicability of these esters in man, because of their effects on the cardiovascular system, basal metabolism and gastric and pancreatic secretions, as well as on the blood sugar. The action of methylacetylcholine on the blood pressure is described.

After reading this monograph one can fully understand the dangers attached to the injudicious use of these substances. One is also left with the impression that the subject requires further investigation, and that a vast amount of work is yet to be done before a full comprehension of the value and effects of these substances can be attained.

The authors list their own works in the bibliography. A complete index of their references to the literature would have made this volume more valuable.

Blood Groups and Blood Transfusion. By Alexander S. Wiener, A.B., M.D. Price, $4. Pp. 220, with 41 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

Since the discovery of the human blood groups by Landsteiner in 1901 much has been learned about the individual differences in blood. This knowledge is of great practical value, especially in transfusion and in solving questions of identity. A number of books have been written about the blood groups, of which this is the most recent. This book aims to include the most recent advances in our understanding of the individual differences of blood and to describe the appropriate technical methods in sufficient detail for practical purposes. After a succinct introduction on blood differences in general comes a detailed account of the four human blood groups. The technic of blood grouping is described fully, also the sources of error in grouping. Blood transfusion is discussed under history, blood grouping, indications, reactions and technic. There is a thorough summary of the present knowledge of the heredity of the blood groups, preceded by a discussion of certain fundamental principles of genetics and biometry. The agglutinogens M and N (Landsteiner and Levine) are the subject of two chapters. Other topics are: the subgroups of groups A and AB, individual differences in human blood demonstrable by other means than typical grouping, group-specific substances in organs and fluids other than blood, blood grouping in relation to clinical medicine and the medicolegal applications of blood groupings. There are indications that blood grouping may become a routine procedure in this country, as it is now in European countries, in cases of disputed paternity. Recently a bill was passed in the state of New York giving courts the power to direct that blood tests be made in suits involving disputed parentage. The methods and value of the individual identification of human blood stains are clearly set forth.

The style is clear and readable. The material is well arranged and presented by a competent hand. Good use is made of tables, and there are forty-one black and white figures. Wiener's book will be welcome to all workers in the field because it gives in a small space a complete and reliable summary of the knowledge of the individual blood differences and its practical applications today.

Books Received

BIOLOGISCHE UNTERSUCHUNGEN ÜBER FARBSTOFFE. Dr. Iwao Matsuo, Professor der Medizin in Kyoto. Band I. Pp. 494. Kyoto, 1934.

ARBEIDER FRA UNIVERSITETETS PATOLOGISK-ANATOMISKE INSTITUT VED RIKSHOSPITALET FOR ÅRET 1934. Bestyrer Prof. Dr. Med. Francis Harbitz. Oslo, Norway, 1935.

PRACTICAL NEUROLOGICAL DIAGNOSIS WITH SPECIAL REFERENCE TO THE PROBLEMS OF NEUROSURGERY. R. Glen Spurling, M.D., Assistant Clinical Professor of Surgery, University of Louisville School of Medicine. Price, $4. Pp. 233, with 99 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

RATS, LICE AND HISTORY: BEING A STUDY IN BIOGRAPHY, WHICH, AFTER TWELVE PRELIMINARY CHAPTERS INDISPENSABLE FOR THE PREPARATION OF THE LAY READER, DEALS WITH THE LIFE HISTORY OF TYPHUS FEVER. Hans Zinsser. Price, $2.75. Pp. 301. Published for the Atlantic Monthly Press. Boston: Little, Brown & Company, 1935.

BLOOD GROUPS AND BLOOD TRANSFUSION. Alexander S. Wiener, A.B., M.D. Price, $4. Pp. 220, with 41 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1933-1934. Presented by the Lord President of the Council to Parliament by Command of His Majesty, January 1935. Price, 3 shillings. Pp. 172. London: His Majesty's Stationery Office, 1935.

PHYSICAL METHODS FOR THE ESTIMATION OF THE DUST HAZARD IN INDUSTRY WITH SPECIAL REFERENCE TO THE OCCUPATION OF THE STONEMASON. H. L. Green and H. H. Watson. Medical Research Council, Special Report Series, no. 199. Price, 1 shilling. Pp. 56, with 14 figures. London: His Majesty's Stationery Office, 1935.

DIE UNSICHTBAREN KRANKHEITSERREGER FILTRIERBARE VIRA: EIN LEHRBUCH FÜR ÄRZTE AND TIERÄRZTE. Dr. Josef Baló, o. ö. Professor der pathologischen Anatomie und Pathohistologie an der Franz-Joseph-Universität, Szeged. Price, 24 marks. Pp. 310, with 39 text figures and 3 color plates. Berlin: S. Karger, 1935.